(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 111 994**
B1

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **26.02.86**

(21) Application number: **83305782.1**

(22) Date of filing: **27.09.83**

(51) Int. Cl.⁴: **C 07 C 87/455**, C 07 D 333/20, C 07 D 307/52, C 07 D 307/14, C 07 D 213/38, C 07 D 295/12, C 07 D 233/54, C 07 D 207/12, C 07 D 249/08, C 07 D 409/12, C 07 D 401/12

(54) **(1-Arylcyclobutyl) alkylamine derivatives, their preparation and their use as therapeutic agents.**

(30) Priority: **30.09.82 GB 8227898**
30.09.82 GB 8227901

(43) Date of publication of application:
27.06.84 Bulletin 84/26

(45) Publication of the grant of the patent:
26.02.86 Bulletin 86/09

(84) Designated Contracting States:
AT BE CH DE FR IT LI LU NL SE

(56) References cited:
GB-A- 973 887
GB-A-2 098 602

CHEMICAL ABSTRACTS, vol. 68, no. 9, February 26, 1968, page 3794, abstract no. 39170j, COLUMBUS OHIO (US), A. KALIR et al.: "1-Phenylcycloalkylamine derivatives"

(73) Proprietor: **The Boots Company PLC**
1 Thane Road West
Nottingham Nottinghamshire NG2 3AA (GB)

(72) Inventor: **Kozlik, Antonin**
4 Hockerwood Clifton Grove
Clifton Nottingham (GB)
Inventor: **Wells, Wilfred Hase**
23 Welbeck Road
Radcliffe-on-Trent Nottinghamshire (GB)

(74) Representative: **Thacker, Michael Anthony et al**
THE BOOTS COMPANY PLC Patents Section R4
Pennyfoot Street
Nottingham NG2 3AA (GB)

EP 0 111 994 B1

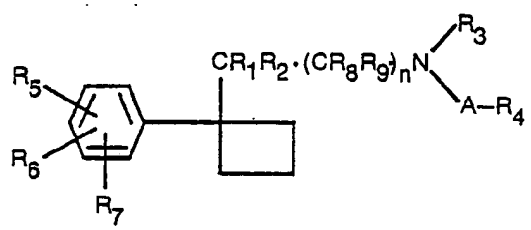
Courier Press, Leamington Spa, England.

Description

This invention relates to (1-arylcyclobutyl)-alkylamine compounds having useful therapeutic activity particularly but not exclusively as antidepressants, to pharmaceutical compositions containing such compounds and to processes for the preparation of such compounds.

(1-Arylcyclobutyl)alkylamine derivatives are described in British Patent 873887 and in a paper by A. Kalier and Z. Pelah [Israel J. Chem. 5 (5) pp 223—9 (1967)] entitled "1-phenylcyclobutylalkylamine derivatives". These disclosures do not describe any antidepressant action for the compounds described therein.

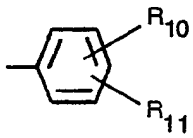
The present invention provides compounds of formula I



I

in which n = 0 or 1;

in which, when n = 0, R_1 is H, a straight or branched chain alkyl group containing 1 to 6 carbon atoms, a cycloalkyl group containing 3 to 7 carbon atoms, a cycloalkylmethyl group in which the cycloalkyl group contains 3 to 7 carbon atoms, an alkenyl group containing 3 to 6 carbon atoms, an alkynyl group containing 3 to 6 carbon atoms, a heterocyclic ring containing one or more heteroatoms selected from N, O and S or a group of formula II;



II

in which, when n = 1, R_1 is H or an alkyl group containing 1 to 3 carbon atoms;

in which R_2 is H or an alkyl group containing 1 to 3 carbon atoms;

in which R_3 is H or a straight or branched chain alkyl group;

in which A is a group of formula III

$$—(CH_2)_x—W—(CH_2)_y—$$ III

in which W is an oxygen atom or a group of formula $—S(O)_m—$ in which m is 0, 1 or 2, a group of formula $—CR_{12}R_{13}—$, a cycloalkylidene group containing 3 to 6 carbon atoms or a cycloalkylene group containing 3 to 6 carbon atoms; x is 0 or an integer from 1 to 5; y is 0 or an integer from 1 to 5 (with the proviso that when W is an oxygen atom or a group of formula $S(O)_m$, x and y are both integers from 1 to 5); R_{12} and R_{13} which are the same or different are H, an alkyl group containing 1 to 3 carbon atoms, hydroxy, methoxy or benzyl;

in which R_4 is a carbocyclic ring, a heterocyclic ring containing one or more heteroatoms selected from N, 0 and S, a cyano group, a carbamoyl group of formula $—CONR_{14}R_{15}$ in which R_{14} and R_{15} which are the same or different are H, an alkyl group containing 1 to 3 carbon atoms or R_{14} and R_{15} together with the nitrogen to which they are attached form a heterocyclic ring, an alkoxycarbonyl group of formula $—COOR_{16}$ in which R_{16} is an alkyl group containing 1 to 3 carbon atoms, an amido group of formula $—N(R_{17})COR_{18}$ in which R_{17} and R_{18}, which may be the same or different, are alkyl groups containing 1 to 4 carbon atoms or R_{17} and R_{18} together with the nitrogen atom and carbonyl group to which they are attached form a ring, an acyloxy group of formula $—OCOR_{19}—$ in which R_{19} is an alkyl group containing 1 to 3 carbon atoms, a hydroxy group, a thiol group, or a group of formula $—OR_{20}$, $—SR_{20}$, $—SOR_{20}$ or SO_2R_{20} in which R_{20} is a straight or branched chain alkyl group containing 1 to 4 carbon atoms or an optionally substituted phenyl group;

in which R_5, R_6 and R_7 which are the same or different, are H, halo, trifluoromethyl, hydroxy, an alkyl group, an alkoxy or alkylthio group, phenyl or R_5 and R_6, together with the carbon atoms to which they are attached, form an optionally substituted second benzene ring;

in which R_8 and R_9, which are the same or different, are H or an alkyl group containing 1 to 3 carbon atoms;

in which R_{10} and R_{11}, which are the same or different, are H, halo, an alkyl group containing 1 to 3 carbon atoms or an alkoxy group containing 1 to 3 carbon atoms;

and pharmaceutically acceptable salts thereof.

When n = 0 and R_1 is an alkyl group the alkyl group contains 1 to 6 carbon atoms (for example methyl, ethyl, propyl, isopropyl, isobutyl, or branched hexyl).

When R_1 is a cycloalkyl group the cycloalkyl ring contains 3 to 7 carbon atoms (for example cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl). When R_1 is a cycloalkylmethyl group the cycloalkyl ring contains 3 to 6 carbon atoms (for example cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl). When R_1 is an alkenyl or alkynyl group, the group contains 3 to 6 carbon atoms (for example allyl or propynyl).

When R_1 is a heterocyclic ring, the ring may contain 5 or 6 atoms and may contain one heteroatom (for example furyl, thienyl, pyrrolyl, pyridyl, tetrahydofuryl or tetrahydrothienyl) or more than one heteroatom which may be the same (for example imidazolyl, pyrazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazolyl, tetrazolyl or dithianyl) or different (for example thiazolyl). The heterocyclic ring may be substituted for example by one or more alkyl groups (for example methyl), halo (for example fluoro or chloro), hydroxy, alkoxy groups (for example methoxy) or trifluoromethyl. In preferred compounds of formula I, R_1 is a furyl, thienyl, pyridyl, tetrahydrofuryl, dithianyl, methylfuryl, methylpyrrolyl, methylimidazolyl, methylpyrazolyl, methyltetrazolyl or methylthiazolyl group.

When R_1 is a group of formula II R_{10} and/or R_{11} may be H, fluoro, chloro, bromo, an alkyl group containing 1 to 3 carbon atoms (for example methyl) or an alkoxy group containing 1 to 3 carbon atoms (for example methoxy).

When n = 1 and R_1 is an alkyl group the alkyl group contains 1 to 3 carbon atoms (for example methyl).

When R_2 is an alkyl group it contains 1 to 3 carbon atoms (for example methyl).

When R_3 is alkyl, the alkyl group contains 1 to 4 carbon atoms (for example methyl, ethyl or propyl).

When the group W is a cycloalkylene or cycloalkylidene group, the group may be cyclohexylene or cyclohexylidene.

When the group R_4 is a carbocyclic ring, the ring may contain 3 to 7 carbon atoms (for example cyclohexyl) and the ring may contain one or more double bonds (for example cycloheptenyl) or the ring may be phenyl optionally substituted by halo (for example fluoro or chloro), hydroxy, alkoxy containing 1 to 3 carbon atoms (for example methoxy) or alkyl containing 1 to 3 carbon atoms (for example methyl).

When R_4 is a heterocyclic ring the ring may contain 5 or 6 atoms. The heterocyclic ring may contain one heteroatom (for example furyl, thienyl, pyrrolyl, pyridyl, tetrahydrofuryl, tetrahydrothienyl, pyrrolinyl, or piperidyl) or more than one heteroatom which may be the same (for example imidazolyl, pyrazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperazinyl, triazolyl, tetrazolyl) or different (for example thiazolyl, isoxazolyl, morpholinyl, thiomorpholinyl or the tetrahydro and dihydro derivatives of thiazolyl or isoxazolyl).

When R_4 is a carbamoyl group of formula —$CONR_{14}R_{15}$ and R_{14} and/or R_{15} is an alkyl group, the alkyl group may be methyl, ethyl, propyl or isopropyl. When R_{14} and R_{19} together with the nitrogen to which they are attached form a heterocyclic ring, the ring may contain 4, 5 or 6 carbon atoms, one or more of which may be replaced by a further heteroatom in addition to the nitrogen atom to which R_{14} and R_{15} are attached.

When R_4 is an alkoxycarbonyl group of formula —$COOR_{16}$, the alkyl group R_{16} may be methyl, ethyl, propyl or isopropyl. When R_4 is an amido group of formula $N(R_{17})COR_{18}$, the alkyl groups R_{17} and R_{18} may be a methyl, ethyl or propyl group or, when R_{17} and R_{18} together with the nitrogen atom and carbonyl group to which they are attached form a ring that ring may contain 5 or 6 atoms (for example oxopyrrolidinyl). When R_4 is an acyloxy group of formula —$OCOR_{19}$, the alkyl group R_{19} may be a methyl, ethyl or propyl group.

When R_4 is a group of formula —OR_{20}, R_{20} may be an alkyl group containing 1 to 4 carbon atoms (for example a methyl, ethyl, propyl, isopropyl, butyl or isobutyl group). When R_4 is a group of formula —SR_{20}, SOR_{20}, or SO_2R_{20}, R_{20} is an alkyl group containing 1 to 3 carbon atoms (for example a methyl group). When R_{20} is a substituted phenyl group the substituent may be halo (for example fluoro or chloro), hydroxy, alkoxy containing 1 to 3 carbon atoms (for example methoxy) or alkyl containing 1 to 3 carbon atoms (for example methyl).

When R_5, R_6 or R_7 are halo the halo group may be fluoro, chloro, bromo or iodo. When R_5, R_6 or R_7 are alkyl, alkoxy or alkylthio groups the group may contain 1 to 3 carbon atoms (for example methyl, methoxy or methylthio). When R_5 and R_6 together with the carbon atoms to which they are attached form a second benzene ring, that second benzene ring may optionally be substituted by halo (for example fluoro, chloro or bromo) or by alkyl or alkoxy groups containing 1 to 3 carbon atoms (for example methyl or methoxy) or the substituents on the second benzene ring together with the carbon atoms to which they are attached form a further benzene ring.

When R_8 and/or R_9 is an alkyl group the group contains 1 to 3 carbon atoms (for example methyl).

When R_{10} and/or R_{11} is halo the halo atom may be fluoro, chloro or bromo. When R_{10} and/or R_{11} is an alkyl or alkoxy group the group contains 1 to 3 carbon atoms (for example methyl or methoxy).

Compounds of formula I may exist as salts with pharmaceutically acceptable acids. Examples of such salts include hydrochlorides, maleates, acetates, citrates, fumarates, tartrates, succinates and salts with dicarboxylic amino acids such as aspartic and glutamic acids. Such salts may exist in the form of solvates (for example hydrates).

Compounds of formula I may contain one or more chiral centres. Compounds having one chiral centre exist in two enantiomeric forms and the present invention includes both enantiomeric forms and mixtures thereof. Compounds having two or more chiral centres exist in diastereoisomeric forms and the present invention includes each of these diastereoisomeric forms and mixtures thereof.

The present invention also includes pharmaceutical compositions containing a therapeutically

effective amount of a compound of formula I together with a pharmaceutically acceptable diluent or carrier.

In therapeutic use, the active compound may be administered orally, rectally, parenterally or topically, preferably orally. Thus the therapeutic compositions of the present invention may take the form of any of the known pharmaceutical compositions for oral, rectal, parenteral or topical administration. Pharmaceutically acceptable carriers suitable for use in such compositions are well known in the art of pharmacy. The compositions of the invention may contain 0.1—90% by weight of active compound. The compositions of the invention are generally prepared in unit dosage form.

Compositions for oral administration are the preferred compositions of the invention and these are the known pharmaceutical forms for such administration, for example tablets, capsules, syrups and aqueous or oily suspensions. The excipients used in the preparation of these compositions are the excipients known in the pharmacists' art. Tablets may be prepared by mixing the active compound with an inert diluent such as calcium phosphate in the presence of disintegrating agents, for example maize starch, and lubricating agents, for example magnesium stearate, and tableting the mixture by known methods. The tablets may be formulated in a manner known to those skilled in the art so as to give a sustained release of the compounds of the present invention. Such tablets may, if desired, be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate. Similarly, capsules, for example hard or soft gelatin capsules, containing the active compound with or without added excipients, may be prepared by conventional means and, if desired, provided with enteric coatings in a known manner. The active ingredient inside the capsule may be formulated in sustained release form. The tablets and capsules may conveniently each contain 1 to 500 mg of the active compound. Other compositions for oral administration include, for example, aqueous suspensions containing the active compound in an aqueous medium in the presence of a non-toxic suspending agent such as sodium carboxymethylcellulose, and oily suspensions containing a compound of the present invention in a suitable vegetable oil, for example arachis oil.

Compositions of the invention suitable for rectal administration are the known pharmaceutical forms for such administration, for example suppositories with cocoa butter or polyethylene glycol bases.

Compositions of the invention suitable for parenteral administration are the known pharmaceutical forms for such administration, for example sterile suspensions in aqueous and oily media or sterile solutions in a suitable solvent.

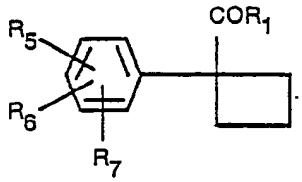
Compositions for topical administration may comprise a matrix in which the pharmacologically active compounds of the present invention are dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally. Alternatively the active compounds may be dispersed in a pharmaceutically acceptable cream or ointment base.

In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example as obtained by fluid energy milling.

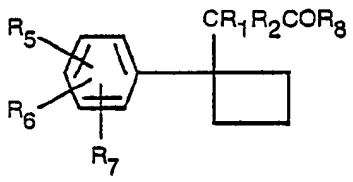
In the compositions of the present invention the active compound may, if desired, be associated with other compatible pharmacologically active ingredients.

The pharmaceutical compositions containing a therapeutically effective amount of a compound of formula I may be used to treat depression in human beings. In such treatment the amount of the compound of formula I administered per day is in the range of 1 to 1000 mg preferably 5 to 500 mg.

Compounds of formula I may be prepared by the reductive amination of ketones or aldehydes of formula IV or V

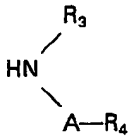


IV



V

by reaction of the ketone or aldehyde with an amine of formula VI



(VI)

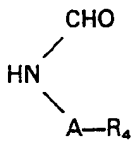
Examples of suitable reductive amination reactions are given below:—

a) by the reaction of the ketone or aldehyde with the amine of formula VI and reducing the resulting imine or enamine for example with sodium borohydride or sodium cyanoborohydride,

b) by the reaction of the ketone or aldehyde with the amine of formula VI in the presence of a reducing agent such as sodium cyanoborohydride or, when R_3 is other than H, in the presence of formic acid,

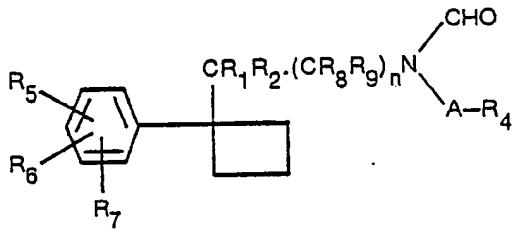
c) when R_1 and R_4 do not contain reducible double bonds, by the catalytic hydrogenation at elevated temperature and pressure of a mixture of the ketone or aldehyde and the amine of formula VI.

Compounds of formula I in which R_3 is H or methyl may be prepared by (a) the reductive amidation of ketones or aldehydes of formula IV or V by the reaction of the ketone or aldehyde with a formamide of formula VII



VII

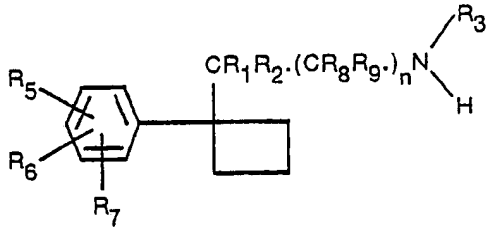
in the presence of formic acid to give compounds of formula VIII



VIII

followed by (b) the hydrolysis, for example acid hydrolysis, of the compounds of formula VIII to give compounds of formula I in which R_3 is H or the reduction of the compounds of formula VIII for example by lithium aluminium hydride or sodium bis(2-methoxyethoxy)aluminium hydride to give compounds of formula I in which R_3 is methyl.

Compounds of formula I may be prepared from amines of formula IX



IX

a) by acylating the amines of formula IX, for example, by reaction with an acyl chloride of formula $R_{21}COCl$ or an anhydride of formula $(R_{21}CO)_2O$ in which R_{21} is a group of formula X

$$—(CH_2)_z—W—(CH_2)_y—R_4 \qquad X$$

in which, when W is an oxygen atom or a group of formula $S(O)_m$, z is an integer from 1 to 4 and, when W is a group of formula $—CR_{12}R_{13}—$, a cycloalkylene group, z is 0 or an integer of 1 to 4 and reducing the resulting amides, for example with lithium aluminium hydride, to give compounds of formula I in which A is a group of formula III in which x is z+1.

b) by reacting the amines of formula IX with aldehydes of formula $R_{21}CHO$ and reducing the resulting imines or enamines for example with sodium cyanoborohydride or, when R_1, R_2, R_4, R_{12} and R_{13} do not contain reducible bonds, by catalytic hydrogenation to give compounds of formula I in which A is a group of formula III in which x is z+1.

c) by reacting the amines of formula IX in which R_3 is other than H with aldehydes of formula $R_{21}CHO$ in the presence of formic acid to give compounds of formula I in which A is a group of formula III in which x is z+1.

d) by reacting the amines of formula IX with ketones of formula $R_{12}CO(CH_2)_yR_4$ and reducing the resulting imines or enamines for example with sodium cyanoborohydride or, when R_1, R_2, R_4 and R_{12} do not contain reducible double bonds, by catalytic hydrogenation to give compounds of formula I in which A is a group of formula XI

$$—CHR_{12}—(CH_2)_y— \qquad XI$$

e) by reacting amines of formula IX in which R_3 is other than H with ketones of formula $R_{12}CO(CH_2)_yR_4$ in the presence of formic acid to give compounds of formula I in which A is a group of formula XI

f) by acylation of the amines of formula IX with, for example, substituted acyl chlorides of formula R_{22}-COCl in which R_{22} is a group of formula XII

$$—(CH_2)_z—W—(CH_2)_y—E \qquad XII$$

wherein E is a replaceable group or is convertible thereto and then either (a) reducing the amides so formed and then replacing the group E with the group R_4 or (b) replacing the group E with the group R_4 and reducing the resulting amides to give compounds of formula I in which A is a group of formula III in which x is z+1. The group E may be for example a halo group which is replaced by the group R_4 by reaction with a compound of formula R_4H, or a salt derived therefrom. The group E may be a hydroxy group which is converted to a *p*-toluenesulphonyloxy group which is then replaced by the group R_4 by reaction with a compound of formula R_4H or a salt derived therefrom.

g) by reacting the amines of formula IX with a compound of formula XIII

$$H_2C{=}CH{-}G \qquad \text{XIII}$$

in which G is as defined above in respect of R_4 or in respect of E. When G has the meaning defined above in respect of E, the resulting compound is converted into a compound of formula I by methods given above. The following are given as examples of processes of this type.

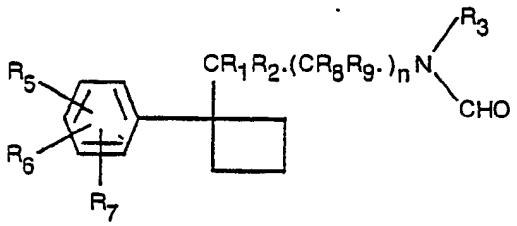
i) by reacting the amines of formula IX with vinylpyridine to give compounds of formula I in which A is an ethylene group and R_4 is a pyridyl group,

ii) by reacting the amines of formula IX with acrylonitrile to give compounds of formula I in which A is an ethylene group and R_4 is a cyano group,

iii) by reacting the amines of formula IX with an alkyl ester of acrylic acid to give compounds of formula I in which A is an ethylene group and R_4 is an alkoxycarbonyl group of formula $-COOR_{16}$.

h) by the reaction of the amines of formula IX with a compound of formula XAR_4 in which X is a leaving group such as a halo group (for example a bromo group) or a *p*-toluenesulphonyloxy group in the presence of a base (for example triethylamine).

Compounds of formula I may be prepared by the reaction of formamides of formula XIV

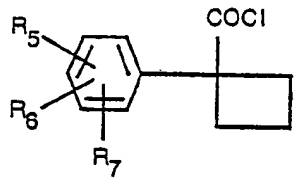


XIV

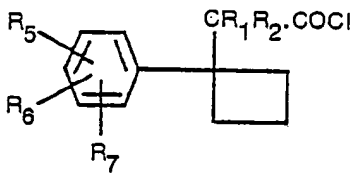
with aldehydes of formula $R_{21}CHO$ in the presence of formic acid to give tertiary amines of formula I when R_3 is other than H or when R_3 is H to give formamides of formula VIII in which A is a group of formula III in which x is z+1 followed by (a) hydrolysis of the formamides of formula VIII, for example acid hydrolysis, to give secondary amines of formula I in which R_3 is H or (b) reduction of the formamides of formula VIII, for example by lithium aluminium hydride or sodium bis(2-methoxyethoxy)aluminium hydride to give tertiary amines of formula I in which R_3 is methyl.

Compounds of formula I may be prepared by the reaction of formamides of formula XIV with ketones of formula $R_{12}CO(CH_2)_yR_4$ in the presence of formic acid to give tertiary amines of formula I when R_3 is other than H, or when R_3 is H to give formamides of formula VIII in which A is a group of formula XI followed by (a) hydrolysis of the formamides of formula VIII, for example acid hydrolysis, to give secondary amines of formula I in which R_3 is H (b) reduction of the formamides of formula VIII for example by lithium aluminium hydride or sodium bis(2-methoxyethoxy)aluminium hydride to give tertiary amines of formula I in which R_3 is methyl.

Compounds of formula I in which n = 0 and R_1 and R_2 are H, and compounds of formula I in which n = 1 and R_8 and R_9 are H may be prepared by the reaction of amines of formula VI with acid derivatives such as esters or acid halides, for example with acid chlorides of formula XV and XVI respectively



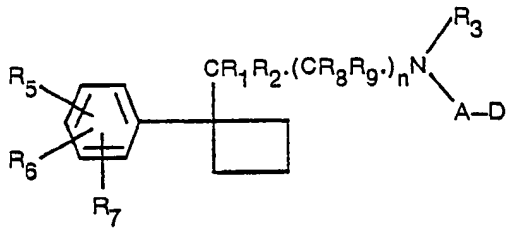
XV



XVI

followed by reduction of the resulting amides for example with lithium aluminium hydride or borane methyl sulphide complex.

When the group R_4 is a heterocyclic ring containing one nitrogen atom in which the nitrogen atom is bonded directly to the group A, compounds of formula I may be prepared by reacting compounds of formula XVII



XVII

in which D is a group of formula NH_2, (a) with a non-geminally disubstituted alkane having at least 2 carbon atoms between the carbon atoms carrying the substituents, which may be halo (for example bromo) or *p*-toluenesulphonyloxy, to give compounds of formula I in which R_4 is a heterocyclic ring containing no heteroatoms other than the nitrogen atom, (b) with a dialkyl ether or thioether in which each alkyl group is substituted by a substituent which may be halo (for example bromo) or *p*-toluenesulphonyloxy to give compounds of formula I in which R_4 is a heterocyclic ring containing an oxygen or sulphur atom in addition to the nitrogen atom or (c) with a dialkylamine in which each alkyl group is substituted by a substituent which may be halo (for example bromo) or *p*-toluenesulphonyloxy to give compounds of formula I in which R_4 is a heterocyclic ring containing a second nitrogen atom.

Compounds of formula I in which R_4 is a carbamoyl group of formula —$CONH_2$ may be prepared from compounds of formula I in which R_4 is cyano for example by hydration with aqueous acids or by reaction with hydrogen peroxide in the presence of a base. Compounds of formula I in which R_4 is an amide group of formula $CONR_{14}R_{15}$ in which one or both of R_{14} and R_{15} are other than H may be prepared by the reaction of amines of formula $HNR_{14}R_{15}$ with carboxylic acid derivatives for example acid chlorides of formula XVII in which D is a group of formula COCl or compounds of formula I in which R_4 is an ester group of formula —$COOR_{16}$.

Compounds of formula I in which R_4 is an alkoxycarbonyl group of formula —$COOR_{16}$ may be prepared by the esterification of carboxylic acids of formula XVII in which D is a group of formula —COOH.

Compounds of formula I in which R_4 is an amido group of formula $N(R_{17})COR_{18}$ may be prepared from compounds of formula XVII in which D is a group of formula —NH_2 by either (a) alkylation to introduce the group R_{17} followed by acylation to introduce the group —COR_{18} or (b) by acylation to introduce the group —COR_{18} followed by alkylation to introduce the group R_{17}.

Compounds of formula I in which R_4 is an acyloxy group of formula $OCOR_{19}$ may be prepared by the acylation of compounds of formula I in which R_4 is hydroxy in the form of a salt.

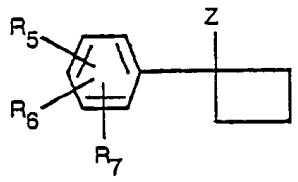
Compounds of formula I in which R_4 is a group of formula SOR_{20} may be prepared by the oxidation of compounds of formula I in which R is SR_{20}. Compounds of formula I in which R_4 is a group of formula SO_2R_{20} may be prepared by the oxidation of compounds of formula I in which R_4 is a group of formula SR_{20} or SOR_{20}. Methods for these oxidations are well known in the art. Compounds of formula I in which R_4 is a group of formula SO_2R_{20} may also be prepared by (a) the oxidation for example using hydrogen peroxide of the product of the reaction between the amines of formula IX and an (alkylthio)-carboxylic acid followed by (b) reduction of the resulting amide for example by borane methyl sulphide complex.

Compounds of formula I in which W is a group of formula $S(O)_m$ and m is 1 may be prepared by the oxidation of compounds of formula I in which m is 0. Compounds of formula I in which m is 2 may be prepared by the oxidation of compounds of formula I in which m is 0 or 1. Methods for these oxidations are well known in the art.

Compounds of formula I may be prepared by the reaction of compounds of formula R_4H or a salt derived therefrom with compounds of formula XVII in which D is a leaving group such as bromo or *p*-toluenesulphonyloxy. Suitable *p*-toluene-sulphonyloxy compounds may be prepared from compounds of formula I in which R_4 is hydroxy.

Processes suitable for the preparation of the amines of formula IX in which R_1 is a group other than a heterocyclic group, the ketones and aldehydes of formula IV in which R_1 is a group other than a heterocyclic group and the ketones and aldehydes of formula V and the formamides of formula XIV in which R_1 is a group other than a heterocyclic group of formula XII are described in British Patent Application 2098602A published after the priority date of the present application. Amines of formula IX, ketones and aldehydes of formula IV and formamides of formula XIV in which R_1 is a heterocyclic group may be prepared by methods analogous to those described in the above identified application.

Amines of formula IX in which R_3 is H may be prepared by the reduction of compounds of formula XVIII



XVIII

in which

a) Z is a group of formula —CR_1=NH to give compounds of formula IX in which n = 0 and R_2 is H;

b) Z is a group of formula —$CONH_2$ to give compounds of formula IX in which n = 0 and R_1 and R_2 are H;

c) Z is a group of formula —CR_1R_2 . CR_8=NH to give compounds of formula IX in which n = 1 and R_9 is H. Suitable reducing agents for the above reactions include sodium borohydride, sodium cyanoborohydride, lithium aluminium hydride or borane-methylsulphide complex.

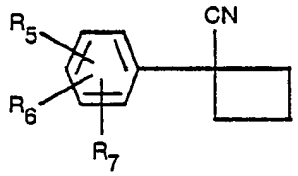
Amines of formula IX in which R_3 is other than H may be prepared by the reduction of compounds of formula XVIII in which Z is a group of formula —$CONHR_3$ to give compounds of formula IX in which n = 0 and R_1 and R_2 are H. Suitable reducing agents for the above reactions include sodium borohydride, sodium cyanoborohydride, lithium aluminium hydride or borane-methylsulphide complex.

Processes suitable for the preparation of acid chlorides of formula XV in which R_1 is a group other than the heterocyclic group and the acid chlorides of formula XVI are described in British Patent Application 2098602A described above. Acid chlorides of formula XV in which R_1 is a heterocyclic group may be prepared by methods analogous to those described in the above identified application.

Compounds of formula XVII may be prepared by similar methods to those described hereinbefore for preparing compounds of formula I but with the R_4 group being replaced by D. Compounds of formula XVII in which A is an ethylene group and D is a group of formula NH_2 may be prepared by the reaction of compounds of formula IX with nitro-ethylene followed by reduction for example with sodium bis(methoxyethoxy)aluminium hydride. Compounds of formula XVII in which A is a propylene group and D is a NH_2 group may be prepared by the reaction of compounds of formula IX with acrylonitrile followed by reduction, for example, with lithium aluminium hydride. Compounds of formula XVII in which A is a propylene group may be prepared by reaction of compounds of formula IX with an ester of acrylic acid followed by (a) reduction of the resulting ester to the corresponding hydroxy compound, (b) replacement of the hydroxy group by a leaving group such as *p*-toluenesulphonyloxy and (c) replacement of the leaving group by the group D. Compounds of formula XVII in which D is an ester or a group of formula COCl may be prepared by compounds of formula XVII in which D is a group of formula —COOH by methods well known in the art. Compounds of formula XVII in which D is a group of formula —COOH may be prepared by hydrolysis, for example acid hydrolysis, of compounds of formula I in which R_4 is a cyano group.

Compounds of formula XVIII in which Z is a group of formula CR_1=NH or CR_1R_2 . R_8=NH may be prepared by the hydrolysis of compounds of formula XVIII in which Z is CR_1=NY and CR_1R_2 . CR_8=NY respectively. In these latter compounds of formula XVIII, Y represents a metal-containing moiety derived from an organometallic reagent such as MgCl or MgBr derived from a Grignard reagent or Li derived from an organolithium compound. Processes suitable for the preparation of these latter compounds in which R_1 is other than a heterocyclic group are described in British Patent Application 2098602A described above. Compounds of formula XVIII in which Z is a group of formula CR_1=NY and R_1 is a heterocyclic group may be prepared by methods analogous to those described in the above identified application.

Compounds of formula XVIII in which Z is a group of formula —$CONH_2$ or —$CONHR_3$ may be prepared by the reaction of acid derivatives (for example acid chlorides of formula XV) with ammonia or an amine of formula R_3NH_2 respectively. Compounds of formula XVIII in which Z is a group of formula $CONH_2$ may be prepared from cyano compounds of formula XIX



XIX

for example by hydration with aqueous acids or by reaction with hydrogen peroxide in the presence of a base.

Processes suitable for the preparation of cyano compounds of formula XIX are described in British Patent Application 2098602A described above.

The therapeutic activity of the compounds of formula I has been indicated by assessing the ability of the compounds to reverse the hypothermic effects of reserpine in the following manner. Male mice of the Charles River CD1 strain weighing between 18 and 30 grammes were separated into groups of five and were supplied with food and water ad libitum. After five hours the body temperature of each mouse was taken orally and the mice were injected intraperitoneally with reserpine (5 mg/kg) in solution in deionised water containing ascorbic acid (50 mg/ml). The amount of liquid injected was 10 ml/kg of body weight. Nine hours after the start of the test food was withdrawn but water was still available ad libitum. Twenty-four hours after the start of the test the temperatures of the mice were taken and the mice were given the test compound suspended in a 0.25% solution of hydroxy ethyl cellulose (sold under the trade name Cellosize QP 15000 by Union Carbide) in deionised water at a dose volume of 10 ml/kg of body weight. Three hours later the temperatures of all the mice were again taken. The percentage reversal of the reserpine-induced loss of body temperature is then calculated by the formula:

$$\frac{(T_{27} - T_{24})}{(T_5 - T_{24})} \times 100$$

in which T_t is the temperature in degrees Celsius after t hours. The mean value for each group of five mice was taken at several dose rates to enable a value of the mean dose which causes a 50% reversal (ED50) to be obtained. All the compounds which are the final products of the Examples hereinafter gave values of ED50 of 30 mg/kg or less. It is widely understood by those skilled in the art that this test is indicative of compounds having antidepressant activity in humans.

The invention will now be illustrated by the following Examples which are given by way of example only. All compounds were characterised by conventional analytical techniques and gave satisfactory elemental analyses. All melting and boiling points are expressed in degrees Celsius.

Example 1

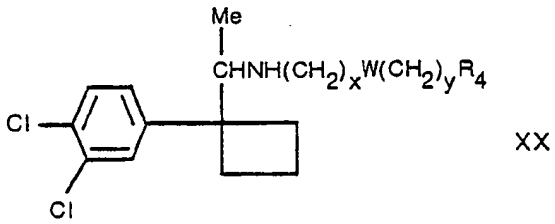
1-Acetyl-1-(3,4-dichlorophenyl)cyclobutane (4.86 g) and benzylamine (2.2 ml) were stirred at a temperature of 140 to 150°C under nitrogen for 1 hour 30 minutes. Methanol (50 ml) was added to the cooled reaction mixture and sodium borohydride (0.8 g) was added over a period of ten minutes. The mixture was stirred at ambient temperature for two hours and then the volume of the reaction mixture was reduced by a half and the mixture poured into water (300 ml). The aqueous mixture was extracted with ether and the ether extract dried and the ether removed by evaporation. The residue was distilled (b.p. 182—186° at 0.5 mm Hg) and the distillate treated with hydrogen chloride in ether to give *N*-benzyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]-ethylamine hydrochloride (m.p. 227—228°C).

Examples 2 to 37

In a similar manner to that described in Example 1 the compounds of formula XX listed in Table 1 and the compounds of formula XXI listed in Table 2 were prepared.

Columns I and II of these Tables show the time in hours and temperature in degrees Celsius at which the reaction between the ketone and the amine took place.

TABLE 1



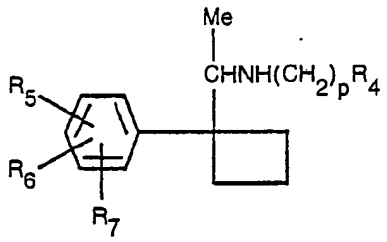
XX

Example Number	x	y	W	R_4	I	II	mp (°C)	Notes
2	0	0	CH_2	2-thienyl	2	140	224—226°	(3)
3	0	0	CH_2	2-pyridyl	2	140	236—238° (dec)	(4)
4	0	0	CH_2	3-pyridyl	2	140	253—255°	(4)
5	0	0	CH_2	4-pyridyl	2	130	234—238° (dec)	(4)
6	0	0	CH_2	2-furyl	2	140	204—207°	(3)
7	0	0	CH_2	2-tetrahydrofuryl	2	130—150		(1)
8	0	1	CH_2	morpholino	2	130	154° (dec)	(4)
9	0	1	CH_2	2-pyridyl	2	130	165° (dec)	(4)
10	0	1	CH_2	4-pyridyl	2	140	198—208°/0.5 mm Hg	(2)
11	0	1	CH_2	piperidino	2	140	164—168°/0.2 mm Hg	(2)
12	0	1	CH_2	phenyl	3	140—150	95° (dec)	(3)
13	0	1	CH_2	4-imidazolyl	3	140	164—170° (dec)	(4)
14	0	1	CH_2	p-chlorophenylthio	4½	140	209—211°/0.1 mm Hg	(2)

TABLE 1 (Continued)

Example Number	x	y	W	R_4	I	II	mp (°C)	Notes
15	0	1	CH_2	cyclohept-1-enyl	16	140	179—180°/0.1 mm Hg	(2)
16	0	1	CH_2	OH	2	140	168–173°	(3)
17	0	1	CH_2	OMe	20	95	145—146°/0.5 mm Hg	(2)
18	0	1	CHMe	phenoxy	4	140	192—194°/0.2 mm Hg	(2)
19	0	1	CHEt	OH	18	140	163°/0.2 mm Hg	(2) (5)
20	0	1	CH_2	CN	5	120—130	200°	(3)
21	0	2	CH_2	1-imidazolyl	2	140	232—236°/0.5 mm Hg	(2)
22	0	2	CH_2	morpholino	2	140	170—175°	(4) (8)
23	0	2	CH_2	1-pyrrolidin-2-onyl	2	140	218—219°	(3)
24	0	2	CH_2	OH	2	140	162—165°	(3) (8)
25	0	2	CH_2	OMe	4	100—120	157°/0.4 mm Hg	(2)
26	0	2	CH_2	OEt	4	125	158°/0.4 mm Hg	(2)
27	0	2	CH_2	O^{i}Pr	18	135	145—146°/0.05 mm Hg	(2)
28	0	2	CH_2	OBu	3	140	180°/0.1 mm Hg	(2)
29	0	3	CH_2	OH	3	140	182°/0.4 mm Hg	(2)
30	1	0	CH(OMe)	OMe	3	130—140	146°/0.4 mm Hg	(2)
31	1	0	CHMe	OH	2	140	184—186° (dec)	(3) (8)
32	1	1	CH(OH)	1,2,4-triazol-1-yl	3	140	257—261°	(4)
33	2	2	O	OH	2	140	180—182°/0.3 mm Hg	(2)
34	2	2	S	OH	3	140	202—205°/0.2 mm Hg	(2)

TABLE 2



XXI

Example Number	R_5	R_6	R_7	p	R_4	I	II	mp (°C)	Notes
35	H	H	H	1	4-pyridyl	2	140	224°	(8) (9)
36	H	H	H	2	morpholino	2	140	147—153°/ 0.4—0.5 mm Hg	(2)
37	4-Cl	H	H	2	morpholino	3	130	148—150° (dec)	(4) (8)

Notes on Tables

(1) product purified by high pressure liquid chromatography. Physical constants not determined.
(2) boiling point of free base.
(3) monohydrochloride salt.
(4) dihydrochloride salt.
(5) L-form.
(6) dimaleate salt
(7) monomaleate salt.
(8) monohydrate.
(9) contains 1.45 moles HCl per mole.
(10) hemihydrate.
(11) physical constants not determined but the structure of the compound was confirmed by conventional analytical techniques.
(12) solvent for the reduction stage was ethanol.
(13) solvent for the reduction stage was methanol.
(14) solvent for the reduction stage was a mixture of ethanol and methanol.

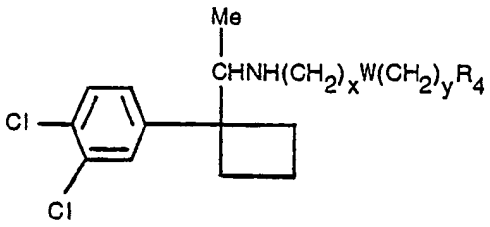
Example 38

1-Acetyl-(3,4-dichlorophenyl)cyclobutane (5.0 g) was added to 2-*n*-propoxyethylamine (1.9 g) and the mixture was stirred and heated to 140—145°C with a slow stream of nitrogen blowing over the reaction to remove the water produced. Heating was continued for 20 hours. The mixture was cooled and a suspension of sodium borohydride (707 mg) in propan-2-ol (60 ml) was added and the mixture heated under reflux for 16 hours. The solvent was removed and the residue was treated with water (150 ml) and the product extracted into ether. The extract was washed with water (10 × 75 ml) dried, filtered and a solution of maleic acid (2.13 g) in ether (100 ml) was added. The mixture was cooled, the resultant solid recrystallised from industrial methylated spirit to give *N*-(2-propoxyethyl)-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine maleate (m.p. 112—114°C).

Example 39

In a similar manner to that described in Example 38 the compounds of formula XX listed in Table 3 and the compounds of formula XXI listed in Table 4 were prepared. The Notes have the same meaning as those given in Tables 1 and 2.

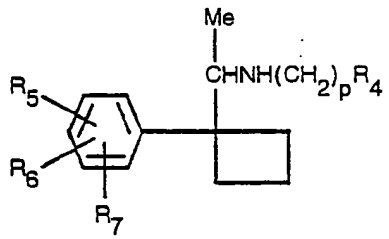
TABLE 3



XX

Example Number	x	y	W	R_4	I	II	mp (°C)	Notes
39	0	1	CH_2	thiomorpholino	24	140	120—122° (dec)	(4)(12)
40	0	1	CHPr	OH	26	160	143—145°	(7)(13)
41	0	2	CMe	OH	20	140	128—130°	(7)
42	2	1	S	phenyl	4	140	163—166°	(3)(12)
43	2	1	S	2-chloro-6-fluorophenyl	20	140	152—154°	(7)
44	2	2	O	OMe	8	110	119—120°	(7)(12)

TABLE 4



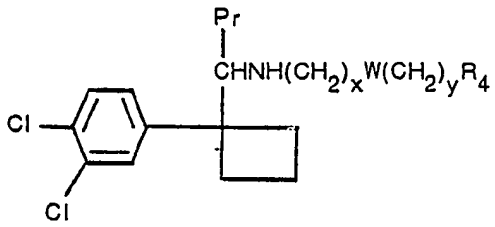
XXI

Example Number	R_5	R_6	R_7	p	R_4	I	II	mp (°C)	Notes
45	4-SMe	H	H	2	morpholino	24	160	156—158°	(6)(13)
46	4-Br	H	H	2	morpholino	8	140	179—180°	(6)(13)
47	4-Ph	H	H	2	morpholino	18	140	145—147°	(6)(13)
48	4-Ph	H	H	2	OH	18	140	103—107°	(7)(13)
49	4-I	H	H	2	OMe	20	95	170—175°	(3)(12)
50	4-I	H	H	2	morpholino	20	140	155—160°	(3)(10)(12)
51	3,4-benzo		H	2	morpholino	6½	150	162—164°	(6)(13)
52	3,4-benzo		H	2	OH	6½	150	110—112°	(7)(13)

Example 53

In a similar manner to that described in either Example 1 or Example 38 the compounds of formula XXII listed in Table 5 and the compounds of formula XXIII listed in Table 6 were prepared. The Notes have the same meanings as those given for Tables 1 and 2.

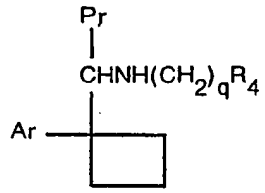
TABLE 5



XXII

Example Number	x	y	W	R_4	I	II	Method	mp (°C)	Notes
53	0	0	CH_2	4-pyridyl	2	135	as Ex. 1	211—213° (dec)	(4) (8)
54	0	0	1,2-cyclo-hexylene	OH	24	160	as Ex. 38	189—191°	(3)(13)
55	0	1	CH_2	morpholino	2½	140	as Ex. 1	246—248°	(4) (8)
56	0	1	CH_2	OPh	16	140	as Ex. 1		(1)
57	0	1	$CH(CH_2Ph)$	OH	24	160	as Ex. 38	144—146° (dec)	(3)(14)
58	1	0	Cyclohexyl-idene	OH	24	160	as Ex. 38	195—196°	(3)(13)
59	0	4	CH_2	OH	12	140	as Ex. 1	201—205°/0.05 mm Hg	(2)
60	2	2	O	OH	5	160	as Ex. 1	198—200°/0.5 mm Hg	(2)
61	2	2	S	OH	3	140	as Ex. 1	190°/0.05 mm Hg	(2)(13)
62	3	2	CH_2	OH	17	160	as Ex. 38	120—123°	(7)(13)
63	4	3	CH_2	OH	17	160	as Ex. 38		(11)(13)

TABLE 6



XXIII

Example Number	Ar	q	R_4	I	II	Method	b.p./m.p.	Notes
64	2-fluorophenyl	2	morpholino	5	140	as Ex. 38	150°/0.01 mm Hg	(2)
65	3-trifluoro-methylphenyl	2	morpholino	4.75	140	as Ex. 38	140°/0.05 mm Hg	(2)
66	6-chloronaphth-2-yl	2	morpholino	18	140	as Ex. 38	168—169°	(6)(13)

Example 67

In a similar manner to that described in Example 38, *N*-(2-methoxyethyl)-1-[1-(3,4-dichlorophenyl)cyclobutyl]-2-methylpropylamine hydrochloride (m.p. 158—160°C) was prepared.

Example 68

A mixture of 1-acetyl-1-(3,4-dichlorophenyl)cyclobutane (2.43 g), glycinamide hydrochloride (2.21 g) powdered potassium hydroxide (1.2 g) and sodium cyanoborohydride (1.5 g) in methanol (20 ml) was stirred at 0—5°C for 2 hours then for a total of 10 days at ambient temperature. The mixture was cooled and 5N hydrochloric acid added. The mixture was then basified, extracted into ether, washed with water, dried and evaporated to give an oil. This oil was dissolved in ether and a solution of maleic acid (1.0 g) in dry

ether (100 ml) was added to give an oil which was dissolved in acetone. Ether was then added to give a white solid which was dissolved in water, basified and extracted into ether. Passing hydrogen chloride gas through the dried ethereal extract gave 2-{1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamino}-acetamide hydrochloride (m.p. 240—245°C).

Example 69

A mixture of 2-(4-methoxyphenoxy)ethylamine (7.0 g) 1-butyryl-1-(3,4-dichlorophenyl)cyclobutane (10.8 g) and dibutyltin dichloride (0.61 g) in dry toluene (20 ml) was stirred and refluxed for 2 hours. Toluene was removed by evaporation and the mixture heated at 175—180°C for a total of 7 hours. The mixture was cooled, dissolved in absolute ethanol (25 ml) then added to a solution of sodium borohydride (5 g) in ethanol (250 ml) and the mixture heated under reflux for 2 hours. The ethanol was evaporated and the mixture acidified, basified and extracted into ether. Passage of hydrogen chloride gas through the dried extracts gave a sticky solid which was partitioned between ether and 5N sodium hydroxide solution. The ether layer was washed with 5N hydrochloric acid, basified, extracted into ether and dried. A solution of maleic acid (3 g) in dry ether (300 ml) was added to give *N*-[2-(4-methoxyphenoxy)ethyl]-1-[1-(3,4-dichlorophenyl)cyclobutyl]butylamine maleate (m.p. 164—166°C).

Example 70

A mixture of the compound of Example 37 in the form of its free base (3.2 g), 98% formic acid (2 ml), 37—40% aqueous formaldehyde (2.8 ml) and water (0.28 ml) was heated at 90 to 95°C for eighteen hours. After cooling, concentrated hydrochloric acid (1 ml) was added and the reaction mixture evaporated to dryness. The residue was triturated with ether to yield *N*-methyl-*N*-(2-morpholinoethyl)-1-[1-(4-chlorophenyl)cyclobutyl]ethylamine dihydrochloride hydrate [m.p. 225—228°C (dec)].

Example 71

A stirred mixture of *p*-anisaldehyde (0.62 ml) and 1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine (see Example 1 of published British Patent Specification 2098602) in the form of its free base (1.22 g) was heated to 130—135° for 30 minutes. After cooling the residue was dissolved in ethanol (10 ml) and the solution added to a solution of sodium borohydride (1.5 g) in ethanol (200 ml). The mixture was heated under reflux for one hour. Water (10 ml) and then excess 5N HCl were added and the ethanol removed by evaporation. The residue was basified with aqueous sodium hydroxide solution and an ether extraction performed. The extract was dried and evaporated to give an oil. Hydrogen chloride gas was passed through an ethereal solution of the oil to give *N*-(4-methoxybenzyl)-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine hydrochloride (m.p. 217—218°C).

Example 72

In a similar manner to that described in Example 71 *N*-(4-fluorobenzyl)-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine hydrochloride (m.p. 244—245°C) was prepared.

Example 73

A solution of *p*-anisaldehyde (6.43 g) and 1-[1-(4-chlorophenyl)cyclobutyl]ethylamine (see Example 1(b) of published British Patent Specification 2098602) in the form of its free base (9.09 g) in dry toluene (50 ml) was heated under reflux for 20 hours under nitrogen and water was removed by means of a Dean-Stark apparatus. The reaction mixture was cooled and solid sodium borohydride (4.1 g) was added. Methanol (40 ml) was added dropwise at a temperature of 25—30°C). The mixture was heated under reflux for one hour and the methanol and toluene removed by evaporation. The residue was cooled to ambient temperature and excess 5N hydrochloric acid added. The mixture was then basified with aqueous sodium hydroxide solution and extracted with ether. The ether extract was washed and shaken with 5N hydrochloric acid to give a white solid which was recrystallised from ethanol to give *N*-(4-methoxybenzyl)-1-[1-(4-chlorophenyl)cyclobutyl]ethylamine hydrochloride (m.p. 225—228°C).

Example 74

A solution of 1-(3,4-dichlorophenyl)-1-cyclobutanecarbonitrile (28.5 g) in dry ether (200 ml) was added dropwise in a nitrogen atmosphere to a stirred mixture of lithium aluminium hydride (6.5 g) and dry ether (200 ml). The mixture was stirred at room temperature for two hours then it was cooled to 10°C. Water (12 ml) and then 15% aqueous sodium hydroxide solution (12 ml) and then water (36 ml) were added. The mixture was filtered through diatomaceous earth (trade name CELITE). The filter was washed with ether and the combined ether phases were washed with water and dried. Hydrogen chloride gas was passed into the solution to give [1-(3,4-dichlorophenyl)cyclobutyl]methylamine hydrochloride (m.p. 271—272°C).

A solution of chloroacetylchloride (3 g) in dry ether was added dropwise to a stirred solution of [1-(3,4-dichlorophenyl)cyclobutyl]methylamine (6.2 g prepared from the hydrochloride salt described above) and triethylamine (2.9 g) in dry ether (20 ml) at a temperature of 5 to 10°C. The mixture was stirred for four hours, filtered and the filtrate washed with water, dried and evaporated to give *N*-(2-chloroacetyl)-[1-(3,4-dichlorophenyl)cyclobutyl]methylamine (m.p. 104—105°C).

A solution of morpholine (1.9 ml) in dry tetrahydrofuran (5 ml) was added dropwise to a solution of the chloroacetyl compound (2.7 g) in dry tetrahydrofuran (10 ml) and the mixture was heated under reflux for

two hours. The mixture was filtered and the filtrate evaporated to dryness. The residue was dissolved in ether and the solution washed with water and dried. Passing hydrogen chloride gas through the dried solution gave *N*-{[1-(3,4-dichlorophenyl)cyclobutyl]methyl}-2-morpholinoacetamide hydrochloride (m.p. 195—198°C).

Borane-methyl sulphide complex (2 ml) was added to a refluxing solution of the morpholinoacetamide prepared in a similar manner to that described above in the form of its free base (3.6 g) in dry tetrahydrofuran (20 ml) and the mixture heated under reflux for four hours. The mixture was cooled and water (10 ml) added. Dimethylsulphide and tetrahydrofuran were removed by evaporation and excess 5N hydrochloric acid added. The solution was basified and extracted with ether. Hydrogen chloride gas was passed into the washed and dried ether extract. Evaporation to dryness gave a residue which was triturated with dry ether and recrystallised from an 8:2 mixture of propan-2-ol and ethanol to give *N*-(2-morpholinoethyl)-[1-(3,4-dichlorophenyl)cyclobutyl]methylamine dihydrochloride monohydrate (m.p. 230—244°C).

Example 75

A solution of chloroacetylchloride (5.5 g) in dry ether (30 ml) was added dropwise to a solution of α-[1-(4-chlorophenyl)cyclobutyl]benzylamine (see Example 16 of published British Patent Specification 2098602) in the form of its free base (11.95 g) and a solution of triethylamine (4.9 g) in dry ether (40 ml) at around 5°C). The mixture was stirred at room temperature for twenty hours and then filtered. The filtrate was washed with water, aqueous sodium bicarbonate solution and water and dried over magnesium sulphate. Morpholine (8.4 g) was added and the mixture heated under reflux for 24 hours. The reaction mixture was extracted with 2N hydrochloric acid and the aqueous fraction washed with ether. Addition of aqueous sodium hydroxide precipitated a solid which was recrystallised from petroleum ether (b.p. 80—100°C) to give *N*-{α-[1-(4-chlorophenyl)cyclobutyl]benzyl}-2-morpholinoacetamide (m.p. 95—97°C).

Borane-methyl sulphide complex (11.5 ml) was added dropwise under nitrogen to a solution of the acetamide prepared above (6 g) in dry tetrahydrofuran (50 ml) heated under reflux. Heating under reflux was continued for 16 hours and excess reducing agent and solvent removed by distillation. The residue was cooled and water (60 ml) and excess 5N hydrochloric acid added. Aqueous sodium hydroxide solution was added with ice-cooling and the mixture extracted with ether. The ether extract was washed and dried and hydrogen chloride gas passed into it to give a precipitate which was dissolved in hot ethanol. Addition of petroleum ether (b.p. 60—80°) precipitated *N*-(2-morpholinoethyl)-α-[1-(4-chlorophenyl)cyclobutyl]-benzylamine dihydrochloride (m.p. 235—240°C).

Example 76

Thionyl chloride (6 ml) was added to 2-[1-(4-chlorophenyl)cyclobutyl]acetic acid (1.5 g) (see Example 38 of published British Patent Specification 2098602) and the mixture heated under reflux for one hour. Excess thionyl chloride was removed *in vacuo* and the residue added dropwise with cooling to a solution of 2-methoxyethylamine (0.99 g) in ether (10 ml). The mixture was stirred for 30 minutes and water added. The ether phase was washed with water, dried and the solvent removed by evaporation to give *N*-(2-methoxyethyl)-2-[1-(4-chlorophenyl)cyclobutyl]acetamide.

Borane-methyl sulphide complex (3.4 ml) was added dropwise to a solution of the acetamide (1.6 g) prepared as described above in dry tetrahydrofuran (30 ml). The mixture was heated under reflux for seven hours and then half the solvent removed by evaporation. A mixture of concentrated hydrochloric acid (5 ml) and water (5 ml) was added dropwise with ice-cooling. Water was added and the aqueous layer washed with ether, cooled in ice, basified with 16N sodium hydroxide solution and extracted with ether. The ether extract was washed, dried and the ether removed by evaporation. Hydrogen chloride gas was passed into a solution of a sample of the residue in ether to give *N*-(2-methoxyethyl)-2-[1-(4-chlorophenyl)cyclobutyl]-ethylamine hydrochloride (m.p. 113—115°C).

Example 77

In a similar manner to that described in Example 76, *N*-(2-methoxyethyl)-2-[1-(2-naphthyl)cyclobutyl]-ethylamine was prepared and isolated as its maleate salt (m.p. 95—99°C) by adding a solution of maleic acid (2.5 g) in ether (500 ml) to a solution of the free base (0.5 g) in ether (20 ml).

Example 78

Dicyclohexylcarbodiimide (3.62 g) was added to a stirred solution of 1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine (see Example 1 of published British Patent Application 2098602) in the form of its free base (4.02 g) and (methylthio)acetic acid (1.8 g) in dichloromethane (100 ml). The mixture was stirred at ambient temperature for six hours then filtered through diatomaceous earth (sold under the trade name CELITE) and the solvent removed by evaporation. Petroleum ether (500 ml b.p. 60—80°) at its boiling point was added and the mixture filtered. The volume of the filtrate was reduced to *ca* 200 ml and the solution was cooled to 0°C. *N*-{1-[1-(3,4-dichlorophenyl)cyclobutyl]ethyl}-2-(methylthio)acetamide (m.p. 88°C) precipitated as white needles.

Borane-methyl sulphide complex (14 ml) was added dropwise to a solution of the acetamide prepared as described above (7.6 g) in dry tetrahydrofuran (10 ml) heated under reflux. Heating was continued for six hours and the mixture was left at room temperature for sixty hours. Crushed ice (200 g) was added

cautiously followed by 5N hydrochloric acid added dropwise to pH 2. The mixture was basified with aqueous sodium hydroxide solution and the volume reduced by evaporation. The mixture was extracted with ether and the extracts washed and dried. Hydrogen chloride gas was passed into the extract and the solvent removed by evaporation. The residue was heated with petroleum ether (b.p. 60—80°C) to give *N*-[2-(methylthio)ethyl]-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine hydrochloride (m.p. 148—150°C).

Example 79

A mixture of the product of Example 78 in the form of its free base (5.7 g), *m*-chloroperbenzoic acid (3.7 g — 85% purity) and dichloromethane (300 ml) was stirred at ambient temperature for 12 hours. The reaction solution was washed with 5N aqueous sodium hydroxide solution and water and then dried. Evaporation of the solvent gave an oil from which *N*-[2-(methylsulphinyl)ethyl]-1-[1-(3,4-dichlorophenyl)-cyclobutyl]ethylamine was separated by high pressure liquid chromatography. The amine was dissolved in dry ether and hydrogen chloride gas passed through the solution to give a gum which was dissolved in ethyl acetate. Heating this solution to 80°C caused the precipitation of *N*-[2-(methylsulphinyl)ethyl]-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine hydrochloride (m.p. 170—171°C).

Example 80

N-{1-[1-(3,4-dichlorophenyl)cyclobutyl]ethyl}-2-(methylthio)acetamide prepared as described in Example 77 (4.1 g) was added to a vigorously stirred solution of sodium tungstate (10 mg) and glacial acetic acid (4 drops) in water (20 ml). 27.5% Aqueous hydrogen peroxide solution (3.2 ml) was added dropwise and the mixture stirred at 80°C for four hours. The reaction mixture was left at ambient temperature for 16 hours. Aqueous ammonia solution (S.G. 0.880 2 ml) was added and then sodium metabisulphite was added in small portions until gas evolution ceased. The mixture was extracted with dichloromethane and the solvent removed to yield a residue which was shown by gas-liquid chromatography (glc) to contain 45% of the desired product. The residue was treated twice in the above procedure until glc showed 85% of the desired product. The final residue was purified by chromatography to give a white solid (m.p. 167—169°) which is believed to be *N*-{1-[1-(3,4-dichlorophenyl)cyclobutyl]ethyl}-2-(methylsulphonyl)acetamide.

Borane-methylsulphide complex (1.34 ml) was added dropwise to a mixture of the acetamide prepared as described above (1.47 g) and tetrahydrofuran (6 ml) heated under reflux. Heating was continued for 3 hours and the mixture was then kept at ambient temperature for 16 hours before being cooled in ice. Water (50 ml) was added dropwise and the solution was made acidic by the addition of 5N hydrochloric acid. After basifying the solution with aqueous sodium hydroxide an ether extraction was performed. Hydrogen chloride gas was passed into the dried ether extract. The ether was removed by evaporation and the residue dissolved in ethyl acetate. *N*-[2-(methylsulphonyl)ethyl]-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine hydrochloride (m.p. 172—174°C) crystallised from the solution.

Example 81

The product of Example 74 in the form of its free base (0.55 g) 98% formic acid (4 ml) and 37—40% aqueous formaldehyde were heated at 70—80°C for four hours. The reaction mixture was cooled and basified with aqueous sodium hydroxide solution. The mixture was then extracted with ether and the ether extract washed and dried. Hydrogen chloride gas was passed through the extract to give *N*-methyl-*N*-(2-morpholinoethyl)-[1-(3,4-dichlorophenyl)cyclobutyl]methylamine dihydrochloride (m.p. 233—235°C).

Example 82

In a similar manner to that described in Example 81 the product of Example 77 in the form of its free base was converted into *N*-(2-methoxyethyl)-*N*-methyl-2-[1-(2-naphthyl)cyclobutyl]ethylamine hydrochloride (m.p. 139—141°C).

Example 83

In a similar manner to that described in Example 81 the product of Example 20 in the form of its free base was converted into *N*-methyl-3-{1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamino}propiononitrile hydrochloride (m.p. 219—220°C).

Example 84

4-Pyridinecarboxaldehyde (2.35 g) was added to a mixture of 1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine (5 g) and dibutyltin dichloride (0.63 g) in toluene (15 ml) and the resulting mixture was heated under reflux for 17 hours. The mixture was cooled and dissolved in ethanol (50 ml). A suspension of sodium borohydride (5 g) in ethanol (250 ml) was added slowly. The mixture was stirred and heated under reflux for 2 hours and was then allowed to cool overnight. Water (75 ml) was added slowly followed by 5N hydrochloric acid (25 ml) and the alcohol was then removed by evaporation. The aqueous residue was cooled and washed with ether. The aqueous solution was basified with 16N aqueous sodium hydroxide and the product extracted with ether. The extracts were washed with water, dried and evaporated to give an oil.

The residue was purified by a process in which the residue was dissolved in toluene (50 ml) and extracted with 5N hydrochloric acid (4×). The extracts were washed with toluene and basified and the product was extracted with ether.

The dried ethereal solution was treated with hydrogen chloride gas to give a solid which was collected, suspended in boiling ethyl acetate and industrial methylated spirit was added to give a clear solution. *N*-(4-pyridylmethyl)-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine dihydrochloride [(m.p. 201—205°C (dec)] crystallised on cooling.

Example 85

1-[1-(4-Methoxyphenyl)cyclobutyl]ethylamine (2.8 g) was heated to 120°C and 4-pyridinecarboxaldehyde (2.1 g) was added and the mixture was heated at 120—200°C for 2 hours. The mixture was allowed to cool and diluted with methanol. Sodium borohydride (1.75 g) was added and the resulting mixture heated under reflux for 2½ hours. After standing at room temperature for 16 hours the mixture was poured into water, treated with 5N hydrochloric acid and then basified with 5N aqueous sodium hydroxide solution. The product was extracted into ether and the ether extracts were washed with water, dried and evaporated to dryness to give a red oil. The oil was purified by distillation and the distillate dissolved in ether and treated with a solution of excess maleic acid in ether to give a white solid and a sticky yellow gum. Recrystallisation of the white solid from propan-2-ol and ether gave *N*-(4-pyridylmethyl)-1-[1-(4-methoxyphenyl)cyclobutyl]ethylamine (1.25) maleate as a pale yellow solid (m.p. 110—113°C).

Example 86

A mixture of 1-[1-(3-chloro-4-methylphenyl)cyclobutyl]butylamine (2.5 g) [see Example 10(k) of British Patent Specification 2098602A] and 4-pyridinecarboxaldehyde (1.5 ml) was stirred and heated at 130°C for 18 hours. The mixture was dissolved in ethanol (50 ml) and the solution added to a solution of sodium borohydride (2.5 g) in ethanol (120 ml) and heated under reflux for 2 hours. Excess ethanol was removed by evaporation and the mixture acidified, basified and extracted into ether. Hydrogen chloride gas was passed through the dried extract to give an oil which was triturated with acetone to give *N*-(4-pyridylmethyl)-1-[1-(3-chloro-4-methylphenyl)cyclobutyl]butylamine dihydrochloride (m.p. 203—206°C).

Example 87

In a similar manner to that described in Example 86 above except that the reduction took place in methanol at ambient temperature, *N*-(4-pyridylmethyl)-1-[1-(4-chlorophenyl)-cyclobutyl]butylamine dihydrochloride (m.p. 228—230°C) was prepared.

Example 88

Sodium borohydride (2.5 g) was added portionwise to a stirred solution of methoxyacetic acid (26.4 g) in toluene (300 ml) under an atmosphere of nitrogen and stirring was continued for 16 hours. A solution of 1-(1-(4-chlorophenyl)cyclobutyl)-3-methylbutylamine (5 g) in toluene (50 ml) was then added and the mixture was heated under reflux with stirring for 24 hours. After cooling the reaction mixture, water (200 ml) was added and the mixture was basified with 16N aqueous sodium hydroxide solution. The product was extracted into ether and the extracts were washed with water, dried and evaporated to give a brown oil which was dissolved in ether (30 ml). A solution of maleic acid (4.8 g) in ether (250 ml) was added. The solid which precipitated was collected, dried and recrystallised from ethyl acetate with hot filtereing to give *N*-(2-methoxyethyl)-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine maleate (m.p. 131—133°C).

Example 89

A solution of 1-phenyl-1-cyclobutanecarbonitrile (30 g) in ether (100 ml) was added dropwise to a stirred solution of cyclohexylmagnesium bromide [prepared from cyclohexyl bromide (62.3 g) and magnesium (9.5 g) in ether (200 ml)]. The ether was replaced with toluene, and the mixture was stirred at 90°C for 24 hours. Sodium borohydride (7.3 g) was added as a slurry in ethanol (200 ml) and the mixture was heated under reflux for 3 hours. The cooled mixture was acidified, basified, diluted with ether and water, and filtered (Celite). The organic layer was separated and the aqueous layer was extracted with ether. The combined extracts were washed, dried and the solvent removed by evaporation to give (cyclohexyl)(1-phenylcyclobutyl)methylamine which was isolated by conversion into a hydrochloride salt.

A solution of dicyclohexylcarbodiimide (2.6 g) in dichloromethane (50 ml) was added dropwise to a stirred solution of (cyclohexyl)(1-phenylcyclobutyl)methylamine prepared from the salt isolated above and methoxyacetic acid (1.13 g) in dichloromethane (50 ml). The mixture was stirred at room temperature for 4 hours and allowed to stand at room temperature for 72 hours and filtered through diatomaceous earth (Celite). The filtrate was evaporated to remove solvent and the residue was boiled with light petroleum (b.p. 60—80°C) (200 ml) and filtered through diatomaceous earth (Celite). The filtrate was evaporated to leave a colourless oil which was distilled to yield *N*-[(cyclohexyl)(1-phenylcyclobutyl)methyl]-2-methoxyacetamide b.p. 146—148°C at 3.5 mm Hg.

Borane-methyl sulphide complex (2.48 ml) was added dropwise to a refluxing solution of the acetamide (2.6 g) prepared above in tetrahydrofuran (6 ml). The mixture was heated under reflux for 2 hours left at room temperature for 16 hours and heated under reflux for 2 hours, cooled in ice, and hydrolysed by the slow dropwise addition of ice-water. The mixture was acidified, basified, and extracted with ether. The washed and dried extracts were evaporated to leave an oil which was purified by high pressure liquid chromatography to give *N*-[(cyclohexyl)(1-phenylcyclobutyl)methyl]-2-methoxyethylamine as a pale yellow oil the physical characteristics of which were not determined.

Example 90

A mixture of 1-[1-(3,4-dichlorophenyl)cyclobutyl)butylamine (2 g), methyl acrylate (2 g) and toluene (10 ml) was heated under reflux with stirring for a total of 20 hours. Methyl acrylate (0.5 ml) was added, and heating under reflux and stirring were continued for 3 days. The solvent was removed *in vacuo*, and the oily residue was purified by chromatography on a silica column using a mixture of 9 parts petroleum ether (b.p. 40—60°) and 1 part acetone as eluant. From the eluate methyl 3-{1-[1-(3,4-dichlorophenyl)cyclobutyl]butylamino}propanoate was obtained as a pale yellow oil, the physical properties of which were not determined.

Example 91

A mixture of 1-[1-(3,4-dichlorophenyl)cyclobutyl]butylamine (2.0 g) and 1,2-epoxybutane (3 ml) was heated in a sealed tube at 90—95°C for 3 days. A further portion of the epoxide (4 ml) was added and the mixture was heated in the sealed tube for a further 3 days.

The reaction mixture was diluted with ether and treated with a solution of maleic acid in ether to give a colourless oil which crystallised to give a white solid which was recrystallised from propan-2-ol to give 1-{1-[1-(3,4-dichlorophenyl)cyclobutyl]butylamino}butan-2-ol maleate (m.p. 120—122°C).

Example 92

A mixture of 2-[1-(3,4-dichlorophenyl)cyclobutyl]acetic acid (1.8 g prepared in a similar manner to that described in Example 38 of British Patent Specification 2098602A for the corresponding 4-chloro compound) and thionyl chloride (6.5 ml) was heated under reflux for 1 hour. Excess thionyl chloride was then evaporated *in vacuo* and the residue was added dropwise to a stirred, ice-cooled solution of 2-methoxyethylamine (1.05 g) in dry ether (10 ml). The resulting mixture was stirred at room temperature for 45 minutes and water (20 ml) was added. The product was extracted with ether and the extracts were combined, dried and evaporated to give *N*-(2-methoxyethyl)-2-[1-(3,4-dichlorophenyl)cyclobutyl]acetamide as an oil.

A solution of the acetamide (2.02 g) in dry ether (18 ml) was added dropwise in an atmosphere of nitrogen to a stirred mixture of lithium aluminium hydride (0.63 g) and dry ether (9 ml). When the addition was complete the mixture was stirred at ambient temperature for 2 hours then at reflux for 3 hours. It was then cooled in ice and water (0.7 ml), 5N aqueous sodium hydroxide (0.7 ml) and water (2.1 ml) were added sequentially. The mixture was stirred for 30 minutes and was filtered and the filtrate extracted with N hydrochloric acid. The acidic extracts were washed with ether and basified and the product was extracted with ether. The extracts were washed with water, dried and evaporated to give an oil which was redissolved in ether and hydrogen chloride was bubbled into the solution to give a colourless solid. The solid was collected and suspended in boiling petroleum ether (b.p. 40—60°C) and then ethyl acetate was added slowly to give a clear solution. *N*-(2-methoxyethyl)-2-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine hydrochloride (m.p. 114.5—116°C) crystallised on cooling.

Example 93

The product of Example 16 (4.0 g) was suspended in ethyl acetate (20 ml) and acetic anhydride (1.3 g) was added. The mixture was heated under reflux for 3½ hours. The solvent was removed by evaporation and residual acetic acid removed azeotropically with toluene. The residue (4.0 g) was dissolved in water (40 ml) and treated with ether (35 ml) and aqueous ammonia (4 ml). The ether layer was separated, dried and evaporated to give an oil (3.2 g) which was dissolved in ether and treated with a solution of maleic acid (1.2 g) in ether (40 ml) to give 2-{1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamino}ethyl acetate maleate.

Example 94

Cyclohexylacetyl chloride (3.21 g) in dry ether (100 ml) was added over 30 minutes to a stirred mixture of 1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine (4.88 g), triethylamine (2.5 g) and dry ether (100 ml) at 0—6°C. After stirring for a further 3 hours the mixture was filtered and the residue was washed with dry ether. The filtrate and washings were combined, dried and evaporated. The residue was dissolved in tetrahydrofuran (50 ml) and the solution heated under reflux in an atmosphere of nitrogen. Borane-methyl sulphide complex (3 ml) was added from a syringe. The resulting mixture was heated under reflux for 12 hours after which it was cooled and ice-water and then 5N hydrochloric acid were added. The organic solvent was removed by evaporation and the residue was cooled, basified with 5N sodium hydroxide solution and extracted with ether. The extracts were washed with water, dried and the ether removed by evaporation. From the residue *N*-(2-cyclohexylethyl)-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine was obtained by distillation (b.p. 170°C/0.5 mm Hg).

Example 95

2-Ethylbutylmagnesium bromide was prepared by adding a solution of 2-ethylbutyl bromide (25.1 g) in dry ether (25 ml) dropwise to a rapidly stirring mixture of magnesium turnings (3.6 g) in dry ether (100 ml) under nitrogen. When all of the magnesium had dissolved, a solution of 1-(3,4-dichlorophenyl)-1-cyclobutanecarbonitrile (23.6 g) in dry ether (50 ml) was added. The ether was gradually replaced by dry toluene (200 ml) and the mixture stirred and heated at 110°C for 1 hour.

A solution of sodium borohydride (6 g) in ethanol (300 ml) was added and the mixture heated under reflux for 4 hours. After cooling the mixture, water and 5N hydrochloric acid were added. The mixture was basified and the organic solvents removed by evaporation. The residual aqueous layer was basified and extracted into ether. The extract was washed, dried and evaporated to give a residue which was distilled at 146—150°C/0.1 mm Hg. 1-[1-(3,4-Dichlorophenyl)cyclobutyl]-3-ethylpentylamine maleate was made by adding a solution of excess maleic acid in ether to a solution of the distilled amine in ether and collecting the white solid.

A solution of dry triethylamine (10.1 g) in dry ether (20 ml) was added dropwise to a stirred mixture of the maleate (18.0 g) prepared as described above in dry ether (100 ml). A solution of methoxyacetylchloride (4.89 g) in dry ether (10 ml) was added dropwise keeping the temperature in the range 5—10°C. The mixture was stirred at room temperature for two hours and then filtered. The filtrate was diluted with water. The ethereal layer was washed with 5N hydrochloric acid, water, dried and the solvent removed by evaporation to give an oil which was purified by chromatography on a florisil column eluted with a 1:1 mixture of ether and petroleum ether (b.p. 40—60°C). *N*-{1-[1-(3,4-Dichlorophenyl)cyclobutyl]-3-ethylpentyl}-2-methoxyacetamide (m.p. 72—74°C) was obtained on standing from the largest of the fractions from the column.

Borane-methyl sulphide complex (2 ml) was added dropwise to a solution of the methoxyacetamide (5 g) prepared as described above in dry tetrahydrofuran (20 ml) at 0—5°C). This mixture was left at ambient temperature for 7 days, then poured onto ice-water basified and extracted into ether, washed with water, dried and evaporated to dryness to give an oil. This oil was treated as above with more borane-methyl sulphide to give *N*-(2-methoxyethyl)-1-[1-(3,4-dichlorophenyl)cyclobutyl]-3-ethyl pentylamine (b.p. 189—190°C/1.5 mm Hg) as an oil.

Example 96

Acetic anhydride (5 ml) and water (5 ml) were added to the product of Example 8 in the form of its free base (1.5 g) and the mixture maintained at 30°C for 2 hours. The mixture was stirred at ambient temperature for 16 hours and then heated to 95°C for 16 hours. The mixture was cooled and poured into ice/water (150 ml). Aqueous sodium hydroxide solution was added and the aqueous solution extracted with ether. The extract was washed, dried and evaporated to give a residue which was triturated with ice-cold petroleum ether (b.p. 60—80°C) and recrystallised from petroleum ether (b.p. 80—100°C) to give *N*-acetyl-*N*-(2-morpholinoethyl)-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine (m.p. 121—122°C) as a white solid.

Borane-methyl sulphide complex (4 ml) was added under a nitrogen atmosphere to a solution of the amide prepared as above (0.63 g) in dry tetrahydrofuran (50 ml). The mixture was stirred for 16 hours. The residue was cooled to 0°C and water (30 ml) added and then 2.5N sodium hydroxide solution (30 ml) added. The basic mixture was extracted with ether and the extract was washed, dried, filtered and evaporated to give an oil which was dissolved in ether and the solution filtered. Passing hydrogen chloride gas through the solution gave *N*-ethyl-*N*-(2-morpholino-ethyl)-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine dihydrochloride hydrate (m.p. 105—115°C).

Example 97

In a similar manner to that described in Example 96 *N*-ethyl-*N*-(2-methoxyethyl)-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine hydrochloride hydrate (m.p. 115—124°C) was prepared from the product of Example 17.

Example 98

In a similar manner to that described in Example 96, *N*-(2-morpholinoethyl)-*N*-propyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine dihydrochloride (2.23 g) hydrate (m.p. 105—115°C) was prepared by the reaction of the product of Example 8 with propionic anhydride followed by reduction of the resulting *N*-propionyl compound.

Example 99

A solution of 2-thienyl bromide (24.5 g) in dry ether (20 ml) was added to a rapidly stirred mixture of magnesium turnings (3.6 g) in dry ether (25 ml). When the magnesium had totally dissolved a solution of 1-(4-chlorophenyl)-1-cyclobutanecarbonitrile (20.2 g) in dry ether (50 ml) was added and the mixture heated under reflux with stirring for 3 hours. A solid precipitated which was separated and dissolved in ethanol (50 ml). A suspension of sodium borohydride (7 g) in ethanol (100 ml) was added and the mixture heated under reflux for 2 hours. 5N Hydrochloric acid was added to the cooled reaction mixture which was basified and extracted with ether. The ether was removed by evaporation and the residue dissolved in ether. Passing hydrogen chloride gas through the dried solution gave [1-(4-chlorophenyl)cyclobutyl](thien-2-yl)methylamine hydrochloride.

4-Pyridinecarboxaldehyde (0.6 g) was added to the product obtained above in the form of its free base (1.4 g) at 110—115°C. The mixture was stirred and heated at 135—140°C for 30 minutes. After the mixture had been cooled to room temperature a solution of sodium borohydride (1 g) in ethanol (50 ml) was added and the mixture heated under reflux for two hours. After cooling excess 5N hydrochloric acid was added and the reaction mixture made basic by adding 5N aqueous sodium hydroxide solution. The ethanol was removed by evaporation and the mixture extracted with ether. The ether extract was washed with water

and dried. Hydrogen chloride gas was passed through the ethereal solution which was then evaporated to dryness. Trituration of the residue with propan-2-ol gave *N*-(4-pyridylmethyl)-[1-(4-chlorophenyl)cyclobutyl](2-thienyl)methylamine dihydrochloride (m.p. 226—230°C).

Example 100

n-Butyllithium (160 ml of a 1.55M solution in hexane) was added dropwise under a nitrogen atmosphere to a cold (0°C) stirred solution of 1-methylimidazole (20 g) in ether (1000 ml) and the mixture was stirred at 0°C for 1 hour. A solution of 1-(3,4-dichlorophenyl)-1-cyclobutanecarbonitrile (50 g) in ether (200 ml) was added dropwise at 0°C and the mixture was stirred at 0°C for 2 hours before being cooled to −40°C. Methanol (50 ml) in ether (100 ml) was added at −40°C to −30°C, then water (100 ml) was added at −30°C, the mixture was allowed to warm to −10°C and a further portion of water (100 ml) was added.

The aqueous layer was extracted with ether and the dried ethereal extracts were added in portions to a hot mixture of sodium borohydride (20 g) and ethanol (500 ml). The ether was evaporated and the mixture heated under reflux for 16 hours and evaporated *in vacuo*. The residue was diluted with water (500 ml), acidified with dilute aqueous hydrochloric acid, basified with dilute aqueous sodium hydroxide, and extracted with ether. The extracts were washed and dried and the solvent removed by evaporation to leave an orange oil which crystallised from petroleum ether (b.p. 40—60°C) to give pale yellow microplates.

The solid was rereduced with sodium borohydride in boiling propan-2-ol to give [1-(3,4-dichlorophenyl)cyclobutyl][2-(1-methylimidazolyl)]methylamine as a viscous yellow oil.

Methoxyacetyl chloride (1.2 g) was added dropwise to a solution of the base prepared as above (3 g) and triethylamine (1.5 g) in ether (50 ml) and the mixture was heated under reflux for two hours and allowed to stand at ambient temperature for sixteen hours. The reaction mixture was poured into water and the resulting mixture was extracted with ether. The ether extracts were washed with water, dried and the ether removed to yield *N*-{[1-(3,4-dichlorophenyl)cyclobutyl][1-methylimidazol-2-yl]methyl}-2-methoxyacetamide.

Borane-methyl sulphide complex (5 ml) was added dropwise to a solution of the acetamide (3.3 g) prepared as above in tetrahydrofuran (100 ml) and the mixture stirred for 2 days. Ice-water was added cautiously and the resulting mixture basified. The basified mixture was extracted with ether and the extracts washed and dried. Removal of the ether gave a residue which was dissolved in ether. Hydrogen chloride gas was passed through the solution to give a hydrochloride of *N*-{[1-(3,4-dichlorophenyl)cyclobutyl][1-methylimidazol-2-yl]methyl}-2-methoxyethylamine containing 1.8 moles of hydrochloride and 1.6 moles of water which decomposed when heated to 150°C.

Example 101

A mixture of the base prepared as described in Example 100 (3 g) and 4-vinylpyridine (1.5 g) was heated at 100°C for 3 days under nitrogen. After standing for 3 days at ambient temperature the reaction mixture was heated under reflux with a mixture of ether (150 ml) and ethyl acetate (150 ml) and filtered hot. The filtrate yielded a brown oil which was dissolved in hot ether and filtered. Hydrogen chloride gas was passed through the cooled solution to give a solid which was basified and purified by column chromatography and recrystallisation from a mixture of ether and petroleum ether (b.p. 40—60°C) to yield *N*-{[1-(3,4-dichlorophenyl)cyclobutyl][1-methylimidazol-2-yl]methyl}-2-(4-pyridyl)ethylamine hydrate (m.p. 110—111°C).

Example 102 to 104

The compound of Example 8 in the form of its free base was converted into the following salts.

Example	Salt	m.p.	Notes
102	dimaleate	160—163°	
103	dicitrate	65—75°	(0.66)hydrate
104	(1.3)tartrate	180—190°	

Example 105

Pharmaceutical compositions containing any one of the compounds of formula I disclosed in Examples 1 to 104 are prepared in the following manner.

Example 105(a)

Tablets are prepared from the following ingredients:

	Parts by Weight
Active Ingredient	50.0
Lactose	78.5
Polyvinylpyrrolidone	5.0
Maize Starch	15.0
Magnesium Stearate	1.5

The active ingredient, the lactose and some of the starch are mixed and granulated with a solution of the polyvinylpyrrolidone in ethanol. The granulate is mixed with the stearic acid and the rest of the starch and the mixture is compressed in a tabletting machine to give tablets containing 50.0 mg of the active ingredient.

Example 105(b)

Capsules are prepared in the following way. A mixture of the active ingredient (45 parts by weight) and lactose powder (205 parts by weight) is filled into hard gelatin capsules, each capsule containing 45 mg of the active ingredient.

Example 105(c)

In the preparation of enteric coated tablets, the tablets described in Example 105(a) are given a thin coat of shellac varnish, followed by 20 coats of cellulose acetate phthalate in a manner well known in the art. In a similar manner the capsules of Example 105(b) may be provided with an enteric coating.

Example 105(d)

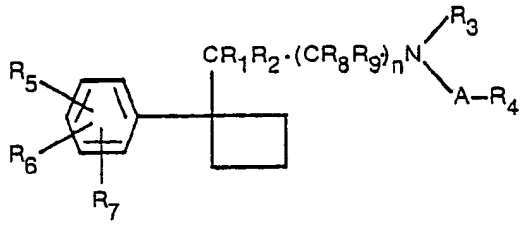
Vials containing a solution of water-soluble compounds of the present invention suitable for injection are prepared from the following ingredients:

Active Ingredient	1100 g
Mannitol	1100 g
Water, freshly distilled	to 11 litres

The active ingredient and mannitol are dissolved in some of the water and the volume of the solution is adjusted to 11 litres. The resulting solution is sterilised by filtration and filled into sterile vials each containing 1.65 ml of solution.

Claims for the contracting states: BE CH DE FR IT LI LU NL SE

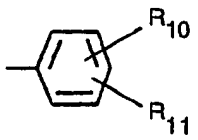
1. Compounds of formula I



I

in which n = 0 or 1;

in which, when n = 0, R_1 is H, a straight or branched chain alkyl group containing 1 to 6 carbon atoms, a cycloalkyl group containing 3 to 7 carbon atoms, a cycloalkylmethyl group in which the cycloalkyl group contains 3 to 7 carbon atoms, an alkenyl group containing 3 to 6 carbon atoms, an alkynyl group containing 3 to 6 carbon atoms, a heterocyclic ring containing one or more heteroatoms selected from N, O and S or a group of formula II;



II

in which, when n = 1, R_1 is H or an alkyl group containing 1 to 3 carbon atoms;
in which R_2 is H or an alkyl group containing 1 to 3 carbon atoms;
in which R_3 is H or a straight or branched chain alkyl group;
in which A is a group of formula III

$$—(CH_2)_x—W—(CH_2)_y—$$ III

in which W is an oxygen atom or a group of formula $—S(O)_m—$ in which m is 0, 1 or 2, a group of formula $—CR_{12}R_{13}—$, a cycloalkylidene group containing 3 to 6 carbon atoms or a cycloalkylene group containing 3 to 6 carbon atoms; x is 0 or an integer from 1 to 5; y is 0 or an integer from 1 to 5 (with the proviso that when W is an oxygen atom or a group of formula $S(O)_m$, x and y are both integers from 1 to 5); R_{12} and R_{13} which are the same or different are H, an alkyl group containing 1 to 3 carbon atoms, hydroxy, methoxy or benzyl;

in which R_4 is a carbocyclic ring, a heterocyclic ring containing one or more heteroatoms selected from N, O and S, a cyano group, a carbamoyl group of formula $—CONR_{14}R_{15}$ in which R_{14} and R_{15} which are the same or different are H, an alkyl group containing 1 to 3 carbon atoms or R_{14} and R_{15} together with the nitrogen to which they are attached form a heterocyclic ring, an alkoxycarbonyl group of formula $—COOR_{16}$ in which R_{16} is an alkyl group containing 1 to 3 carbon atoms, an amido group of formula $—N(R_{17})COR_{18}$ in which R_{17} and R_{18}, which may be the same or different, are alkyl groups containing 1 to 4 carbon atoms or R_{17} and R_{18} together with the nitrogen atom and carbonyl group to which they are attached form a ring, an acyloxy group of formula $—OCOR_{19}—$ in which R_{19} is an alkyl group containing 1 to 3 carbon atoms, a hydroxy group, a thiol group, or a group of formula $—OR_{20}$, $—SR_{20}$, $—SOR_{20}$ or SO_2R_{20} in which R_{20} is a straight or branched chain alkyl group containing 1 to 4 carbon atoms or an optionally substituted phenyl group;

in which R_5, R_6 and R_7 which are the same or different, are H, halo, trifluoromethyl, hydroxy, an alkyl group, an alkoxy or alkylthio group, phenyl or R_5 and R_6, together with the carbon atoms to which they are attached, form an optionally substituted second benzene ring;

in which R_8 and R_9, which are the same or different, are H or an alkyl group containing 1 to 3 carbon atoms;

in which R_{10} and R_{11}, which are the same or different, are H, halo, an alkyl group containing 1 to 3 carbon atoms or an alkoxy group containing 1 to 3 carbon atoms;

and pharmaceutically acceptable salts thereof.

2. Compounds of formula I as claimed in claim 1 wherein R_1 is a methyl, ethyl, propyl, isopropyl, isobutyl, branched hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, allyl or propynyl group or a heterocyclic ring selected from a furyl, thienyl, pyrrolyl, pyridyl, tetrahydrofuryl, tetrahydrothienyl, imidazolyl, pyrazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazolyl, tetrazolyl, dithianyl or thiazolyl ring, said heterocyclic ring being optionally substituted by one or more alkyl groups, containing 1 to 3 carbon atoms, one or more halo groups, one or more alkoxy groups containing 1 to 3 carbon atoms or one or more trifluoromethyl groups.

3. Compounds of formula I in which W is a group of formula $—CR_{12}R_{13}—$ and $R_{12}—$ and R_{12} is a methyl, ethyl or propyl group and R_{13} is H or a methyl group.

4. Compounds of formula I as claimed in claim 1 in which R_4 is a cyclohexyl group, a cycloheptenyl group or phenyl optionally substituted by halo, hydroxy, alkoxy containing 1 to 3 carbon atoms or alkyl containing 1 to 3 carbon atoms.

5. Compounds of formula I as claimed in claim 1 in which R_4 is a heterocyclic ring and is furyl, thienyl, pyrrolyl, pyridyl, tetrahydrofuryl, tetrahydrothienyl, pyrrolinyl, piperidyl, imidazolyl, pyrazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperazinyl, triazolyl, tetrazolyl, thiazolyl, isoxazolyl, morpholinyl, thiomorpholinyl or the tetrahydro and dihydro derivatives of thiazolyl or isoxazolyl.

6. Compounds of formula I as claimed in claim 1 in which R_4 is a group of formula $—OR_{20}$ in which R_{20} is a methyl, ethyl, propyl, isopropyl, butyl or isobutyl group.

7. Compounds of formula I as claimed in any one of the preceding claims wherein R_5, R_6 and R_7 which may be the same or different are selected from the group consisting of H, fluoro, chloro, bromo, iodo, methyl, methoxy and methylthio groups or R_5 and R_6 together with the carbon atoms to which they are attached form a second benzene ring optionally substituted by one or more halo groups, one or more alkyl groups containing 1 to 3 carbon atoms, one or more alkoxy groups containing 1 to 3 carbon atoms or the substitutents on the second benzene ring together with the carbon atoms to which they are attached form a further benzene ring.

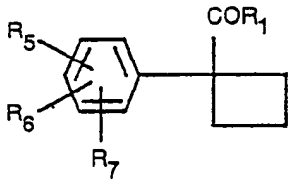
8. Compounds of formula I as claimed in claim 7 wherein the substituents on the second benzene ring are fluoro, chloro, bromo, methyl or methoxy groups.

9. Compound of formula I as claimed in claim 7 wherein R_5 is a halo group, a methyl group, a methylthio group or a phenyl group and R_6 is H or a halo group or R_5 and R_6 together with the carbon atoms to which they are attached form a second benzene ring.

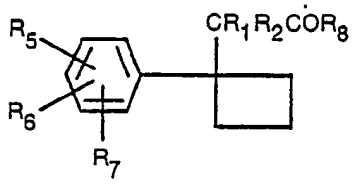
10. Pharmaceutical composition comprising a therapeutically effective amount of a compond of formula I as claimed in any one of claims 1 to 9 together with a pharmaceutically acceptable diluent or carrier.

11. Pharmaceutical compositions as claimed in claim 10 in unit dosage form.

12. A process for the preparation of compounds of formula I comprising the reductive amination of a ketone or aldehyde of formula IV or V

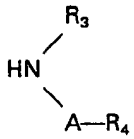


IV



V

by the reaction of the ketone or aldehyde with an amine of formula VI.



VI

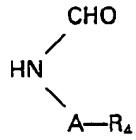
13. A process as claimed in claim 12 wherein the reductive amination takes place:—

a) by the reaction of the ketone or aldehyde with the amine of formula VI and reducing the resulting imine or enamine for example with sodium borohydride or sodium cyanoborohydride,

b) by the reaction of the ketone or aldehyde with the amine of formula VI in the presence of a reducing agent such as sodium cyanoborohydride or, when R_3 is other than H, in the presence of formic acid,

c) when R_1 and R_4 do not contain reducible double bonds, by the catalytic hydrogenation at elevated temperature and pressure of a mixture of the ketone or aldehyde and the amine of formula VI.

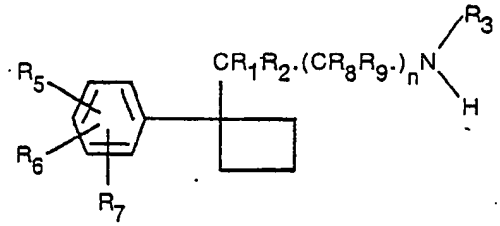
14. A process for the preparation of compounds of formula I in which R_1 is H or methyl comprising the reductive amidation of ketones or aldehydes of formula IV or V by reaction with a formamide of formula VII



VII

in the presence of formic acid followed by a) hydrolysis of the resulting formamide to give compounds of formula I in which R_3 is H or b) reduction of the resulting formamide to give compounds of formula I in which R_3 is methyl.

15. A process for the preparation of compounds of formula I from compounds of formula IX



IX

comprising:—

a) by acylating the amines of formula IX, for example, by reaction with an acyl chloride of formula $R_{21}COCl$ or an anhydride of formula $(R_{21}CO)_2O$ in which R_{21} is a group of formula X

$$—(CH_2)_z—W—(CH_2)_y—R_4 \qquad X$$

in which, when W is an oxygen atom or a group of formula $S(O)_m$, z is an integer from 1 to 4 and, when W is a group of formula $—CR_{12}R_{13}—$, a cycloalkylene group, z is 0 or an integer of 1 to 4 and reducing the resulting amides, to give compounds of formula I in which A is a group of formula III in which x is z+1.

b) by reacting the amines of formula IX with aldehydes of formula $R_{21}CHO$ and reducing the resulting

imines or enamines or, when R_1, R_2, R_4, R_{12} and R_{13} do not contain reducible bonds, by catalytic hydrogenation to give compounds of formula I in which A is a group of formula III in which x is z+1.

c) by reacting the amines of formula IX in which R_3 is other than H with aldehydes of formula $R_{21}CHO$ in the presence of formic acid to give compounds of formula I in which A is a group of formula III in which x is z+1.

d) by reacting the amines of formula IX with ketones of formula $(R_{12}CO(CH_2)_yR_4$ and reducing the resulting imines or enamines or, when R_1, R_2, R_4 and R_{12} do not contain reducible double bonds, by catalytic hydrogenation to give compounds of formula I in which A is a group of formula XI

$$—CHR_{12}—(CH_2)_y— \qquad XI$$

e) by reacting amines of formula IX in which R_3 is other than H is ketones of formula $R_{12}CO(CH_2)_yR_4$ in the presence of formic acid to give compounds of formula I in which A is a group of formula XI

f) by acylating the amines of formula IX with, for example, substituted acyl chlorides of formula R_{22}—COCl in which R_{22} is a group of formula XII

$$—(CH_2)_z—W—(CH_2)_y—E \qquad XII$$

wherein E is a replaceable group or is convertible thereto and then either (a) reducing the amides so formed and then replacing the group E with the group R_4 or (b) replacing the group E with the group R_4 and reducing the resulting amides to give compounds of formula I in which A is a group of formula III in which x is z+1.

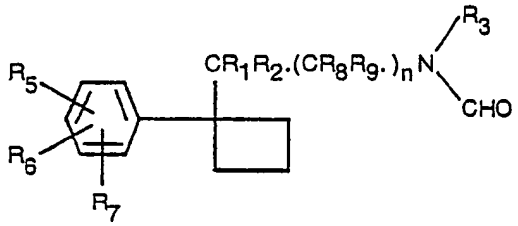
g) by reacting the amines of formula IX with a compound of formula XIII

$$H_2C=CH—G \qquad XIII$$

in which G is as defined above in respect of R_4 or in respect of E and, when G has the meaning defined above in respect of E, converting the resulting compound into a compound of formula I.

h) by the reacting the amines of formula IX with a compound of formula XAR_4 in which X is a leaving group in the presence of a base.

16. A process for the preparation of compounds of formula I in which R_3 is H or methyl by the reaction of formamides of formula XIV

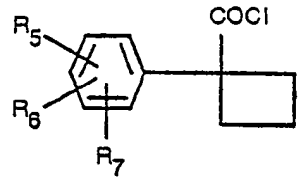


XIV

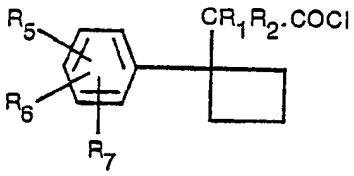
with aldehydes of formula $R_{21}CHO$ in which R_{21} is as defined above or with ketones of formula $R_{12}CO(CH_2)_yR_4$ in the presence of formic acid followed by a) hydrolysis of the resulting formamide to give compounds of formula I in which R_3 is H or b) reduction of the resulting formamide to give compounds of formula I in which R_3 is methyl.

17. A process for the preparation of compounds of formula I comprising the reaction of amines of formula VI with carboxylic acid esters or acid chlorides, followed by reduction of the resulting amide.

18. A process as claimed in claim 17 wherein the amine of formula VI is reacted with an acid chloride of of formula XV or XVI.



XV



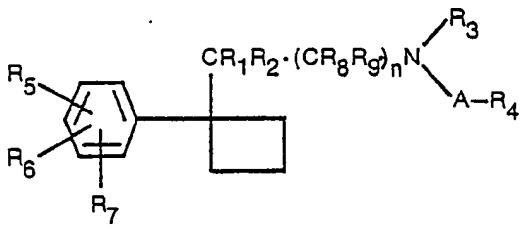
XVI

19. Compounds of formula I as claimed in any one of claims 1 to 9 for use in the treatment of depression.

20. Pharmaceutical compositions as claimed in either claim 10 or claim 11 for use in the treatment of depression.

Claims for the Contracting State: AT

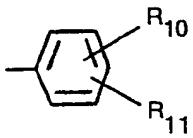
1. A process for the preparation of compounds of formula I



I

in which n = 0 or 1;

in which, when n = 0, R_1 is H, a straight or branched chain alkyl group containing 1 to 6 carbon atoms, a cycloalkyl group containing 3 to 7 carbon atoms, a cycloalkylmethyl group in which the cycloalkyl group contains 3 to 7 carbon atoms, an alkenyl group containing 3 to 6 carbon atoms, an alkynyl group containing 3 to 6 carbon atoms, a heterocyclic ring containing one or more heteroatoms selected from N, O and S or a group of formula II;



II

in which, when n = 1, R_1 is H or an alkyl group containing 1 to 3 carbon atoms;

in which R_2 is H or an alkyl group containing 1 to 3 carbon atoms;

in which R_3 is H or a straight or branched chain alkyl group;

in which A is a group of formula III

$$—(CH_2)_x—W—(CH_2)_y—$$ III

in which W is an oxygen atom or a group of formula $—S(O)_m—$ in which m is 0, 1 or 2, a group of formula $—CR_{12}R_{13}—$, a cycloalkylidene group containing 3 to 6 carbon atoms or a cycloalkylene group containing 3 to 6 carbon atoms; x is 0 or an integer from 1 to 5; y is 0 or an integer from 1 to 5 (with the proviso that when W is an oxygen atom or a group of formula $S(O)_m$, x and y are both integers from 1 to 5); R_{12} and R_{13} which are the same or different are H, an alkyl group containing 1 to 3 carbon atoms, hydroxy, methoxy or benzyl;

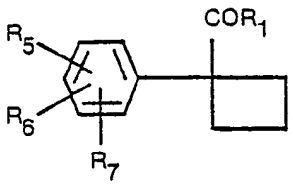
in which R_4 is a carbocyclic ring, a heterocyclic ring containing one or more heteroatoms selected from N, O and S, a cyano group, a carbamoyl group of formula $—CONR_{14}R_{15}$ in which R_{14} and R_{15} which are the same or different are H, an alkyl group containing 1 to 3 carbon atoms or R_{14} and R_{15} together with the nitrogen to which they are attached form a heterocyclic ring, an alkoxycarbonyl group of formula $—COOR_{16}$ in which R_{16} is an alkyl group containing 1 to 3 carbon atoms, an amido group of formula $—N(R_{17})COR_{18}$ in which R_{17} R_{18}, which may be the same or different, are alkyl groups containing 1 to 4 carbon atoms or R_{17} and R_{18} together with the nitrogen atom and carbonyl group to which they are attached form a ring, an acyloxy group of formula $—OCOR_{19}—$ in which R_{19} is an alkyl group containing 1 to 3 carbon atoms, a hydroxy group, a thiol group, or a group of formula $—OR_{20}$, $—SR_{20}$, $—SOR_{20}$ or SO_2R_{20} in which R_{20} is a straight or branched chain alkyl group containing 1 to 4 carbon atoms or an optionally substituted phenyl group;

in which R_5, R_6 and R_7 which are the same or different, are H, halo, trifluoromethyl, hydroxy, an alkyl group, an alkoxy or alkylthio group, phenyl or R_5 and R_6, together with the carbon atoms to which they are attached, form an optionally substituted second benzene ring;

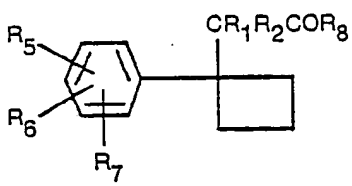
in which R_8 and R_9, which are the same or different, are H or an alkyl group containing 1 to 3 carbon atoms;

in which R_{10} and R_{11}, which are the same or different, are H, halo, an alkyl group containing 1 to 3 carbon atoms or an alkoxy group containing 1 to 3 carbon atoms;

comprising the reductive amination of a ketone or aldehyde of formula IV or V

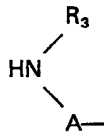


IV



V

by the reaction of the ketone or aldehyde with an amine of formula VI.



VI

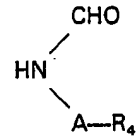
2. A process as claimed in claim 1 wherein the reductive amination takes place:—

a) by the reaction of the ketone or aldehyde with the amine of formula VI and reducing the resulting imine or enamine for example with sodium borohydride or sodium cyanoborohydride,

b) by the reaction of the ketone or aldehyde with the amine of formula VI in the presence of a reducing agent such as sodium cyanoborohydride or, when R_3 is other than H, in the presence of formic acid,

c) when R_1 and R_4 do not contain reducible double bonds, by the catalytic hydrogenation at elevated temperature and pressure of a mixture of the ketone or aldehyde and the amine of formula VI.

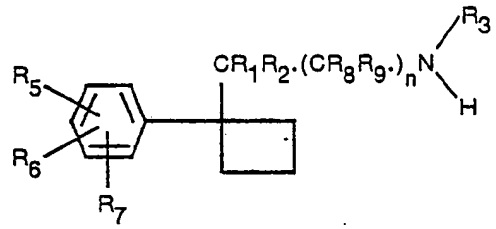
3. A process for the preparation of compounds of formula I in which R_3 is H or methyl comprising the reductive amidation of ketones or aldehydes of formula IV or V by reaction with a formamide of formula VII



VII

in the presence of formic acid followed by a) hydrolysis of the resulting formamide to give compounds of formula I in which R_3 is H or b) reduction of the resulting formamide to give compounds of formula I in which R_3 is methyl.

4. A process for the preparation of compounds of formula I from compounds of formula IX



IX

comprising:—

a) by acylating the amines of formula IX, for example, by reaction with an acyl chloride of formula $R_{21}COCl$ or an anhydride of formula $(R_{21}CO)_2O$ in which R_{21} is a group of formula X

$$—(CH_2)_z—W—(CH_2)_y—R_4 \qquad X$$

in which, when W is an oxygen atom or a group of formula $S(O)_m$, z is an integer from 1 to 4 and, when W is a group of formula $—CR_{12}R_{13}—$, a cycloalkylene group, z is 0 or an integer of 1 to 4 and reducing the resulting amides, to give compounds of formula I in which A is a group of formula III in which x is z+1.

b) by reacting the amines of formula IX with aldehydes of formula $R_{21}CHO$ and reducing the resulting imines or enamines or, when R_1, R_2, R_4, R_{12} and R_{13} do not contain reducible bonds, by catalytic hydrogenation to give compounds of formula I in which A is a group of formula III in which x is z+1.

c) by reacting the amines of formula IX in which R_3 is other than H with aldehydes of formula $R_{21}CHO$ in the presence of formic acid to give compounds of formula I in which A is a group of formula III in which x is z+1.

d) by reacting the amines of formula IX with ketones of formula $R_{12}CO(CH_2)_yR_4$ and reducing the resulting imines or enamines or, when R_1, R_2, R_4 and R_{12} do not contain reducible double bonds, by catalytic hydrogenation to give compounds of formula I in which A is a group of formula XI

$$—CHR_{12}—(CH_2)_y— \qquad XI$$

e) by reacting amines of formula IX in which R_3 is other than H with ketones of formula $R_{12}CO(CH_2)_yR_4$ in the presence of formic acid to give compounds of formula I in which A is a group of formula XI

f) by acylating the amines of formula IX with, for example, substituted acyl chlorides of formula $R_{22}—COCl$ in which R_{22} is a group of formula XII

$$—(CH_2)_z—W—(CH_2)_y—E \qquad XII$$

wherein E is a replaceable group or is convertible thereto and then either (a) reducing the amides so formed and then replacing the group E with the group R_4 or (b) replacing the group E with the group R_4 and reducing the resulting amides to give compounds of formula I in which A is a group of formula III in which x is z+1.

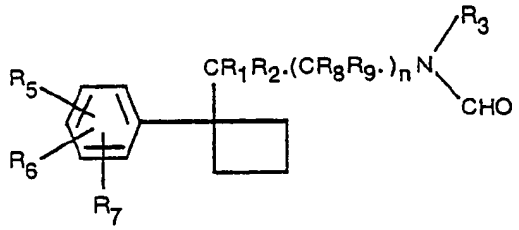
g) by reacting the amines of formula IX with a compound of formula XIII

$$H_2C{=}CH{-}G \qquad \text{XIII}$$

in which G is as defined above in respect of R_4 or in respect of E and, when G has the meaning defined above in respect of E, converting the resulting compound into a compound of formula I.

h) by reacting the amines of formula IX with a compound of formula XAR_4 in which X is a leaving group in the presence of a base.

5. A process for the preparation of compounds of formula I in which R_3 is H or methyl by the reaction of formamides of formula XIV

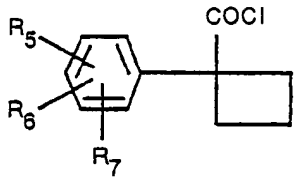


XIV

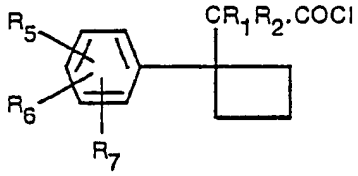
with aldehydes of formula $R_{21}CHO$ in which R_{21} is as defined above or with ketones of formula $R_{12}CO(CH_2)_yR_4$ in the presence of formic acid followed by a) hydrolysis of the resulting formamide to give compounds of formula I in which R_3 is H or b) reduction of the resulting formamide to give compounds of formula I in which R_3 is methyl.

6. A process for the preparation of compounds of formula I comprising the reaction of amines of formula VI with carboxylic acid esters or acid chlorides, followed by reduction of the resulting amide.

7. A process as claimed in claim 6 wherein the amine of formula VI is reacted with an acid chloride of formula XV or XVI



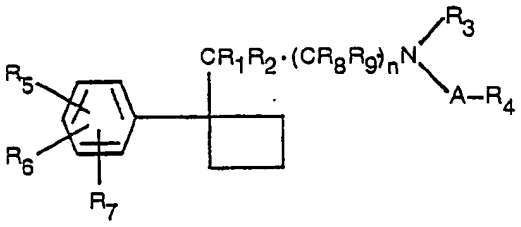
XV



XVI

Patentansprüche für die Vertragsstaaten: BE CH DE FR IT LI LU NL SE

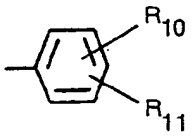
1. Verbindungen der Formel I



I

in der n = 0 oder 1;

in der, wenn n = 0, R_1 H, eine geradkettige oder verzweigte Alkylgruppe mit 1 bis 6 Kohlenstoffatomen, eine Cycloalkylgruppe mit 3 bis 7 Kohlenstoffatomen, eine Cycloalkylmethylgruppe, in der die Cycloalkylgruppe 3 bis 7 Kohlenstoffatome enthält, eine Alkenylgruppe mit 3 bis 6 Kohlenstoffatomen, eine Alkynylgruppe mit 3 bis 6 Kohlenstoffatomen, ein heterocyclischer Ring mit einem oder mehreren Heteroatomen, ausgewählt aus N, O und S oder eine Gruppe der Formel II ist,



II

in der, wenn n = 1, R_1 H oder eine Alkylgruppe mit 1 bis 3 Kohlenstoffatomen ist;
in der R_2 H oder eine Alkylgruppe mit 1 bis 3 Kohlenstoffatomen ist;
in der R_3 H oder eine geradkettige oder verzweigte Alkylgruppe ist;
in der A eine Gruppe der Formel III ist,

$$—(CH_2)_y—W—(CH_2)_y— \quad \text{III}$$

in der W ein Sauerstoffatom oder eine Gruppe der Formel $—S(O)_m—$ ist, in der m 0, 1 oder 2 ist, eine Gruppe der Formel $—CR_{12}R_{13}—$, eine Cycloalkylidengruppe mit 3 bis 6 Kohlenstoffatomen oder eine Cycloalkylengruppe mit 3 bis 6 Kohlenstoffatomen; x ist 0 oder eine ganze Zahl von 1 bis 5; y ist 0 oder eine ganze Zahl von 1 bis 5 (mit der Maßgabe, daß, wenn W ein Sauerstoffatom oder eine Gruppe der Formel $S(O)_m$ ist, x und y eine ganze Zahl zwischen 1 und 5 bedeuten); R_{12} und R_{13}, die gleich oder verschieden sind, sind H, eine Alkylgruppe mit 1 bis 3 Kohlenstoffatomen, Hydroxy, Methoxy oder Benzyl;

in der R_4 ein carbocyclischer Ring, ein heterocyclischer Ring mit einem oder mehreren Heteroatomen, ausgewählt aus N, O und S, eine Cyanogruppe, eine Carbamoylgruppe der Formel $—CONR_{14}R_{15}$ ist, in der R_{14} und R_{15}, die gleich oder verschieden sind, Wasserstoff, eine Alkylgruppe mit 1 bis 3 Kohlenstoffatomen bedeuten oder R_{14} und R_{15} bilden zusammen mit dem Stickstoff, an den sie gebunden sind, einen heterocyclischen Ring, eine Alkoxycarbonylgruppe der Formel $—COOR_{16}$, in der R_{16} eine Alkylgruppe mit 1 bis 3 Kohlenstoffatomen, eine Amidogruppe der Formel $—N(R_{17})COR_{18}$, in der R_{17} und R_{18} gleich oder verschieden sein können, Alkylgruppen mit 1 bis 4 Kohlenstoffatomen sind oder R_{17} und R_{18} bilden zusammen mit dem Stickstoffatom und der Carbonylgruppe, an die sie gebunden sind, einen Ring, eine Acyloxygruppe der Formel $—OCOR_{19}—$, in der R_{19} eine Alkylgruppe mit 1 bis 3 Kohlenstoffatomen, eine Hydroxygruppe, eine Thiolgruppe oder eine Gruppe der Formel $—OR_{20}$, $—SR_{20}$, SOR_{20} oder SO_2R_{20} ist, in der R_{20} eine geradkettige oder verzweigte Alkylgruppe mit 1 bis 4 Kohlenstoffatomen oder eine gegebenenfalls substituierte Phenylgruppe ist;

in der R_5, R_6 und R_7, die gleich oder verschieden sind, Halogen, Trifluormethyl, Hydroxy, eine Alkylgruppe, eine Alkoxy- oder Alkylthiogruppe, Phenyl bedeuten oder R_5 und R_6 bilden mit den Kohlenstoffatomen, an die sie gebunden sind, einen gegebenenfalls substituierten zweiten Benzolring;

in der R_8 und R_9, die gleich oder verschieden sind, H oder eine Alkylgruppe mit 1 bis 3 Kohlenstoffatomen bedeuten;

in der R_{10} und R_{11}, die gleich oder verschieden sind, H, Halogen, eine Alkylgruppe mit 1 bis 3 Kohlenstoffatomen oder eine Alkoxygruppe mit 1 bis 3 Kohlenstoffatomen sind;

und die pharmazeutisch akzeptablen Salze.

2. Verbindungen der Formel I gemäß Anspruch 1, in der R_1 Methyl, Ethyl, Propyl, Isopropyl, Isobutyl, verzweigtes Hexyl, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Cyclopropylmethyl, Cyclobutylmethyl, Cyclopentylmethyl, Cyclohexylmethyl, Allyl oder eine Propinylgruppe oder ein heterocyclischer Ring ist, ausgewählt aus Furyl, Thienyl, Pyrrolyl, Pyridyl, Tetrahydrofuryl, Tetrahydrothienyl, Imidazolyl, Pyrazolyl, Pyrazinyl, Pyrimidinyl, Pyridazinyl, Triazolyl, Tetrazolyl, Dithianyl oder Thiazolyl, wobei der heterocyclische Ring gegebenenfalls durch eine oder mehrere Alkylgruppen mit 1 bis 3 Kohlenstoffatomen, eine oder mehrere Halogengruppen, eine oder mehrere Alkoxygruppen mit 1 bis 3 Kohlenstoffatomen oder eine oder mehrere Trifluoromethylgruppen substituiert ist.

3. Verbindungen der Formal I, in der W eine Gruppe der Formel $—CR_{12}R_{13}—$ ist und R_{12} Methyl, Ethyl oder Propyl, und R_{13} Wasserstoff oder Methyl ist.

4. Verbindungen der Formel I nach Anspruch 1, in der R_4 eine Cyclohexylgruppe, eine Cycloheptenylgruppe oder eine gegebenenfalls durch Halogen, Hydroxy, Alkoxy mit 1 bis 3 Kohlenstoffatomen oder Alkyl mit 1 bis 3 Kohlenstoffatomen substituierte Phenylgruppe bedeutet.

5. Verbindungen der Formel I nach Anspruch 1, in der R_4 ein heterocyclischer Ring ist und Furyl, Thienyl, Pyrrolyl, Pyridyl, Tetrahydrofuryl, Tetrahydrothienyl, Pyrrolinyl, Piperidyl, Imidazolyl, Pyrazolyl, Pyrazinyl, Pyrimidinyl, Pyridazinyl, Imidazolidinyl, Imidazolinyl, Pyrazolidinyl, Pyrazolinyl, Piperazinyl, Triazolyl, Tetrazolyl, Thiazolyl, Isoxasolyl, Morpholinyl, Thiomorpholinyl oder die Tetrahydro- und Dihydroderivate des Thiazolyls oder Isoxazolyls bedeutet.

6. Verbindungen der Formel I nach Anspruch 1, in der R_4 eine Gruppe der Formel $—OR_{20}$ ist, in der R_{20} eine Methyl-, Ethyl-, Propyl-, Isopropyl-, Butyl- oder Isobutylgruppe ist.

7. Verbindungen der Formel I nach Anspruch 1 bis 6, in der R_5, R_6 und R_7, die gleich oder verschieden sein können, ausgewählt aus der Gruppe bestehend aus H, Fluor, Chlor, Brom, Jod, Methyl, Methoxy und Methylthiogruppen oder R_5 und R_6 bilden zusammen mit den Kohlenstoffatomen, an die sie gebunden sind, einen zweiten Benzolring, der gegebenenfalls durch eine oder mehrere Halogengruppen, eine oder mehrere Alkylgruppen mit 1 bis 3 Kohlenstoffatomen, eine oder mehrere Alkoxygruppen mit 1 bis 3 Kohlenstoffatomen substituiert ist, oder die Substituenten im zweiten Benzolring bilden zusammen mit den Kohlenstoffatomen, an die sie gebunden sind, einen weiteren Benzolring.

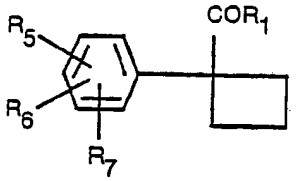
8. Verbindungen der Formel I nach Anspruch 7, in der die Substituenten im zweiten Benzolring Fluor, Chlor, Brom, Methyl oder Methoxygruppen sind.

9. Verbindungen der Formel I nach Anspruch 7, worin R_5 eine Halogengruppe, eine Methylgruppe eine Methylthiogruppe oder eine Phenylgruppe ist und R_6 Wasserstoff oder eine Halogengruppe ist, oder R_5 und R_6 bilden zusammen mit den Kohlenstoffatomen, an die sie gebunden sind, einen zweiten Benzolring.

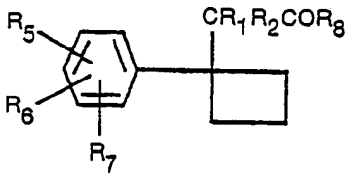
10. Pharmazeutische Zusammensetzung, enthaltend eine therapeutisch wirksame Menge einer Verbindung der Formel I nach Anspruch 1 bis 9, in Verbindung mit einem pharmazeutisch akzeptablen Verdünnungsmittel oder Träger.

11. Pharmazeutisch Zusammensetzung nach Anspruch 10 in Form einer Einzeldosis.

12. Verfahren zur Herstellung der Verbindungen der Formel 1, bestehend aus der reduktiven Aminierung eines Ketons oder Aldehyds der Formel IV oder V

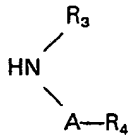


IV



V

durch die Reaktion des Ketons oder Aldehyds mit einem Amin der Formel VI.



VI

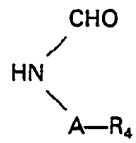
13. Verfahren nach Anspruch 12, wobei die reduktive Aminierung stattfindet:

a) durch die Reaktion eines Ketons oder Aldehyds mit einem Amin der Formel VI und Reduzierung des erhaltenen Imins oder Enamins, z.B. mit Natriumborhydrid oder Natriumcyanoborhydrid,

b) durch die Reaktion eines Ketons oder Aldehyds mit dem Amin der Formel VI in Gegenwart eines Reduktionsmittels, wie z.B. Natriumcyanborhydrid oder, wenn R_3 nicht H bedeutet, in Gegenwart von Ameisensäure.

c) wenn R_1 und R_4 keine reduzierbaren Doppelbindungen enthalten, durch katalytische Hydrogenierung einer Mischung des Ketons oder Aldehyds und des Amins der Formel VI bei erhöhter Temperatur und Druck.

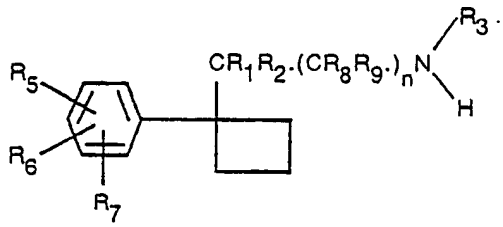
14. Verfahren zur Herstellung der Verbindungen der Formel I, in der R_3 Wasserstoff oder Methyl ist, bestehend aus der reduktiven Amidierung von Ketonen oder Aldehyden der FOrmel IV oder V durch Reaktion mit einem Formamid der Formel VII



VII

In Gegenwart von Ameisensäure, gefolgt von a) Hydrolyse des entstandenen Formamids, um die Verbindungen der Formel I, in der R_3 H ist, zu erhalten, oder b) Reduzierung der entstandenen Formamide, um die Verbindungen der Formel I zu erhalten, in der R_3 Methyl ist.

15. Verfahren zur Herstellung der Verbindungen der Formel I aus Verbindungen der Formel IX



IX

bestehend aus

a) der Acylierung von beispielsweise der Amine der Formel IX durch Reaktion mit einem Acylchlorid der Formel ($R_{21}COCl$ oder einem Anhydrid der Formel $(R_{21}CO)_2O$, worin R_{21} eine Gruppe der Formel X bedeutet

$$—(CH_2)_z—W—(CH_2)_y—R_4 \qquad X$$

in der, wenn W eine Sauerstoffatom oder eine Gruppe der Formel $S(O)_m$ bedeutet, z eine ganze Zahl von 1 bis 4 ist und, wenn W eine Gruppe der Formel $—CR_{12}R_{13}—$, eine Cycloalkylengruppe bedeutet, z 0 oder eine ganze Zahl von 1 bis 4 bedeutet und Reduzierung der erhaltenen Amide, um die Verbindungen der Formel I zu erhalten in der A eine Gruppe der Formel III ist, in der x z+1 ist,

b) der Reaktion der Amine der Formel IX mit Aldehyden der Formel $R_{21}CHO$ und Reduzierung der entstandenen Imine oder Enamine oder, wenn R_1, R_2, R_4, R_{12} und R_{13} keine reduzierbaren Bindungen enthalten, durch katalytische Hydrogenierung, um die Verbindungen der Formel I zu erhalten, worin A eine Gruppe der Formel III ist, in der x z+1 ist.

c) der Reaktion der Amine der Formel IX, in der R_3 von Wasserstoff verschieden ist, mit Aldehyden der Formel $R_{21}CHO$ in Gegenwart von Ameisensäure, um die Verbindungen der Formel I zu erhalten, worin A eine Gruppe der Formel III bedeutet, in der x z+1 ist.

d) der Reaktion der Amine der Formel IX mit den Ketonen der Formel $R_{12}CO(CH_2)_yR_4$ und Reduzierung der entstandenen Imine oder Enamine oder, wenn R_1, R_2, R_4 und R_{12} keine reduzierbaren Doppelbindungen enthalten, durch katalytische Hydrogenierung, um die Verbindungen der Formel I zu erhalten, in der A eine Gruppe der Formel XI bedeutet;

$$—CHR_{12}—(CH_2)_y— \qquad XI$$

e) der Reaktion der Amine der Formel IX, worin R_3, von H verschieden ist, mit den Ketonen der Formel $R_{12}CO(CH_2)_yR_4$ in Gegenwart von Ameisensäure, um die Verbindungen der Formel I zu erhalten, worin A eine Gruppe der Formel XI bedeutet;

f) durch Acylierung der Amine der Formel IX mit, z.B., substituierten Acylchloriden der Formel $R_{22}—COCl$, worin R_{22} eine Gruppe der Formel XII bedeutet

$$—(CH_2)_z—W—(CH_2)_y—E \qquad XII$$

worin E eine austauschbare Gruppe oder eine, in eine austauschbare Gruppe überführbare Gruppe, bedeutet und dann entweder (a) Reduzierung der so gebildeten Amide und anschließender Austausch der Gruppe E gegen die Gruppe R_4 oder (b) Austausch der Gruppe E gegen die Gruppe R_4 und Reduzierung der entstandenen Amide um die Verbindungen der Formel I zu erhalten, worin A eine Gruppe der Formel III ist, in der x z+1 ist.

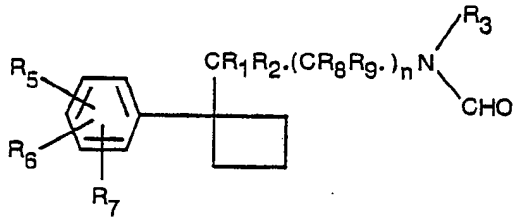
g) der Reaktion der Amine der Formel IX mit einer Verbindung der Formel XIII

$$H_2C=CH—G \qquad XIII$$

in der G die oben angegebene Bedeutung bezüglich R_4 oder bezüglich E aufweist und, wenn G die vorhin gegebene Bedeutung bezüglich E aufweist, Überführung der erhaltenen Verbindung in eine Verbindung der Formel I.

h) der Reaktion der Amine der Formel IX mit einer Verbindung der Formel XAR_4, in der X eine austretende Gruppe in Gegenwart einer Base bedeutet.

16. Verfahren zur Herstellung der Verbindungen der Formel I, in der R_3 H oder Methyl bedeutet, durch Reaktion der Formamide der Formel XIV

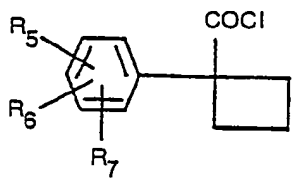


XIV

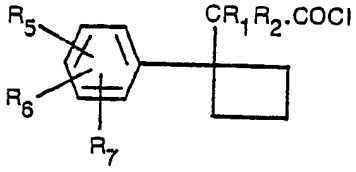
mit Aldehyden der Formel $R_{21}CHO$, worin R_{21} die vorhin gegebene Bedeutung aufweist, oder mit Ketonen der Formel $R_{12}CO(CH_2)_yR_4$ in Gegenwart von Ameisensäure, gefolgt von a) Hydrolyse der erhaltenen Formamide, um die Verbindungen der Formel I zu erhalten, worin R_3 H ist oder b) Reduzierung der erhaltenen Formamide, um die Verbindungen der Formel I zu erhalten, worin R_3 Methyl ist.

17. Verfahren zur Herstellung der Verbindungen der Formel I, bestehend aus der Reaktion der Amine der Formel VI mit Carbonsäureestern oder Säurechloriden, gefolgt von einer Reduzierung der entstandenen Amide.

18. Verfahren nach Anspruch 17, worin das Amin der Formel VI mit einem Säurechlorid der Formel XV oder XVI umgesetzt wird.



XV



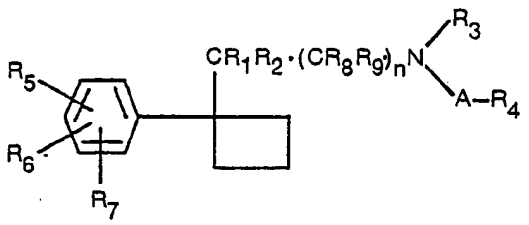
XVI

19. Verbindungen der Formel I nach Anspruch 1 bis 9 zur Verwendung in der Behandlung von Depressionen.

20. Pharmazeutisch Zusammensetzung nach Anspruch 10 oder 11 zur Verwendung in der Behandlung von Depressionen.

Patentansprüche für den Vertragsstaat: AT

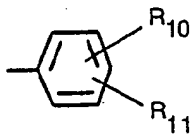
1. Verfahren zur Herstellung von Verbindungen der Formel I



I

in der n = 0 oder 1;

in der, wenn n = 0, R_1 H, eine geradkettige oder verzweigte Alkylgruppe mit 1 bis 6 Kohlenstoffatomen, eine Cycloalkylgruppe mit 3 bis 7 Kohlenstoffatomen, eine Cycloalkylmethylgruppe, in der die Cycloalkylgruppe 3 bis 7 Kohlenstoffatome enthält, eine Alkenylgruppe mit 3 bis 6 Kohlenstoffatomen, eine Alkynylgruppe mit 3 bis 6 Kohlenstoffatomen, eine Heterocyclischer Ring mit einem oder mehreren Heteroatomen, ausgewählt aus N, O und S oder eine Gruppe der Formel II ist,



II

in der, wenn n = 1, R_1 H oder eine Alkylgruppe mit 1 bis 3 Kohlenstoffatomen ist;
in der R_2 H oder eine Alkylgruppe mit 1 bis 3 Kohlenstoffatomen ist;
in der R_3 H oder eine geradkettige oder verzweigte Alkylgruppe ist;
in der A eine Gruppe der Formel III ist,

$$—(CH_2)_x—W—(CH_2)_y—$$ III

in der W ein Sauerstoffatom oder eine Gruppe der Formel $—S(O)_m—$ ist, in der m 0, 1 oder 2 ist, eine Gruppe der Formel $—CR_{12}R_{13}—$, eine Cycloalkylidengruppe mit 3 bis 6 Kohlenstoffatomen oder eine Cycloacylengruppe mit 3 bis 6 Kohlenstoffatomen; x is 0 oder eine ganze Zahl von 1 bis 5; y is 0 oder eine ganze Zahl von 1 bis 5 (mit der Maßgabe, daß, wenn W ein Sauerstoffatom oder eine Gruppe der Formel $S(O)_m$ ist, x und y eine ganze Zahl zwischen 1 und 5 bedeuten); R_{12} und R_{13}, die gleich oder verschieden sind, sind H, eine Alkylgruppe mit 1 bis 3 Kohlenstoffatomen, Hydroxy, Methoxy oder Benzyl;

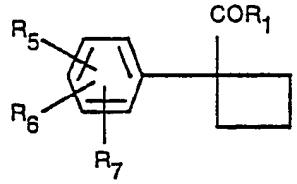
in der R_4 ein carbocyclischer Ring, ein heterocyclischer Ring mit einem oder mehreren Heteroatomen, ausgewählt aus N, O und S, eine Cyanogruppe, eine Carbamoylgruppe der Formel $—CONR_{14}R_{15}$ ist, in der R_{14} und R_{15}, die gleich oder verschieden sind, Wasserstoff, eine Alkylgruppe mit 1 bis 3 Kohlenstoffatomen bedeuten oder R_{14} und R_{15} bilden zusammen mit dem Stickstoff, an den sie gebunden sind, einen heterocyclischen Ring, eine Alkoxycarbonylgruppe der Formel $—COOR_{16}$, in der R_{16} eine Alkylgruppe mit 1 bis 3 Kohlenstoffatomen, eine Amidogruppe der Formel $—N(R_{17})COR_{18}$, in der R_{17} und R_{18} gleich oder verschieden sein können, Alkylgruppen mit 1 bis 4 Kohlenstoffatomen sind oder R_{17} und R_{18} bilden zusammen mit dem Stickstoffatom und der Carbonylgruppe, an die sie gebunden sind, einen Ring, eine Acyloxygruppe der Formel $—OCOR_{19}—$, in der R_{19} eine Alkylgruppe mit 1 bis 3 Kohlenstoffatomen, eine Hydroxygruppe, eine Thiolgruppe oder eine Gruppe der Formel $—OR_{20}$, $—SR_{20}$, SOR_{20} oder SO_2R_{20} ist, in der R_{20} eine geradkettige oder verzweigte Alkylgruppe mit 1 bis 4 Kohlenstoffatomen oder eine gegebenenfalls substituierte Phenylgruppe ist;

in der R_5, R_6 und R_7, die gleich oder verschieden sind, Halogen, Trifluormethyl, Hydroxy, eine Alkylgruppe, eine Alkoxy- oder Alkylthiogruppe, Phenyl bedeuten oder R_5 und R_6 bilden mit den Kohlenstoffatomen, an die sie gebunden sind, einen gegebenenfalls substituierten zweiten Benzolring;

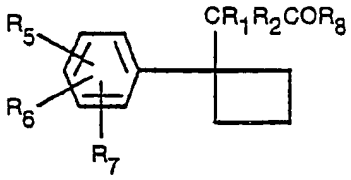
in der R_8 und R_9, die gleich oder verschieden sind, H oder eine Alkylgruppe mit 1 bis 3 Kohlenstoffatomen bedeuten;

in der R_{10} und R_{11}, die gleich oder verschieden sind, H, Halogen, eine Alkylgruppe mit 1 bis 3 Kohlenstoffatomen oder eine Alkoxygruppe mit 1 bis 3 Kohlenstoffatomen sind;

bestehend aus der reduktiven Aminierung eines Ketons oder Aldehyds der Formel IV oder V

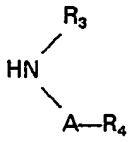


IV



V

durch die Reaktion des Ketons oder Aldehyds mit einem Amin der Formel VI.



VI

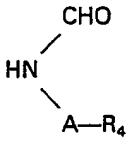
2. Verfahren nach Anspruch 1, wobei die reduktive Aminierung stattfindet:

a) durch die Reaktion eines Ketons oder Aldehyds mit einem Amin der FOrmel Vi und Reduzierung de erhaltenen Imins oder Enamins, z.B. mit Natriumborhydrid oder Natriumcyanoborhydrid,

b) durch die Reaktion eines Ketons oder Aldehyds mit dem Amin der Formel VI in Gegenwart eines Reduktionsmittels, wie z.B. Natriumcyanborhydrid oder, wenn R_3 nicht H bedeutet, in Gegenwart von Ameisensäure,

c) wenn R_1 und R_4 keine reduzierbaren Doppelbindungen enthalten, durch katalytische Hydrogenierung einer Mischung des Ketons oder Aldehyds und des Amins der Formel VI bei erhöhter Temperatur und Druck.

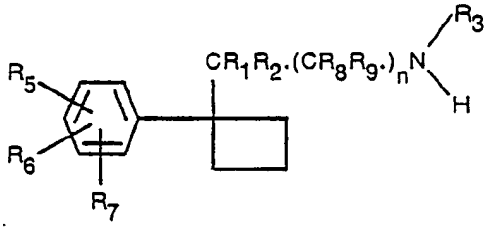
3. Verfahren zur Herstellung der Verbindung der Formel I, in der R_3 Wasserstoff oder Methyl ist, bestehend aus der reduktiven Amidierung von Ketonen oder Aldehyden der Formel IV oder V durch Reaktion mit einem Formamid der Formel VII



VII

in Gegenwart von Ameisensäure, gefolgt von a) Hydrolyse des entstandenen Formamids, um die Verbindungen der Formel I, in der R_3 H ist, zu erhalten, oder b) Reduzierung der entstandenen Formamide, um die Verbindungen der Formel I zu erhalten, in der R_3 Methyl ist.

4. Verfahren zur Herstellung der Verbindungen der Formel I aus Verbindungen der Formel IX



IX

bestehend aus

a) der Acylierung von beispielsweise der Amine der Formel IX durch Reaktion mit einem Acylchlorid der Formel $R_{21}COCl$ oder einem Anhydrid der Formel $(R_{21}CO)_2O$, worin R_{21} eine Gruppe der Formel X bedeutet

$$—(CH_2)_z—W—(CH_2)_y—R_4 \qquad X$$

in der, wenn W ein Sauerstoffatom oder eine Gruppe der Formel $S(O)_m$ bedeutet, z eine ganze Zahl von 1 bis 4 ist und, wenn W eine Gruppe der Formel $—CR_{12}R_{13}—$, eine Cycloalkylengruppe bedeutet, z 0 oder eine ganze Zahl von 1 bis 4 bedeutet und Reduzierung der erhaltenen Amide, um die Verbindungen der Formel I zu erhalten, in der A eine Gruppe der Formel III ist, in der x z+1 ist,

b) der Reaktion der Amine der Formel IX mit Aldehyden der Formel $R_{21}CHO$ und Reduzierung der entstandenen Imine oder Enamine oder, wenn R_1, R_2, R_4, R_{12} und R_{13} keine reduzierbaren Bindungen enthalten, durch katalytische Hydrogenierung, um die Verbindungen der Formel I zu erhalten, worin A eine Gruppe der Formel III ist, in der x z+1 ist.

c) der Reaktion der Amine der Formel IX, in der R_3 von Wasserstoff verschieden ist, mit Aldehyden der Formel $R_{21}CHO$ in Gegenwart von Ameisensäure, um die Verbindungen der Formel I zu erhalten, worin A eine Gruppe der Formel III bedeutet, in der x z+1 ist.

d) der Reaktion der Amine der Formel IX mit den Ketonen der Formel $R_{12}CO(CH_2)_yR_4$ und Reduzierung der entstandenen Imine oder Enamine oder, wenn R_1, R_2, R_4 und R_{12} keine reduzierbaren Doppelbindungen enthalten, durch katalytische Hydrogenierung, um die Verbindungen der Formel I zu erhalten, in der A eine Gruppe der Formel XI bedeutet;

$$—CHR_{12}—(CH_2)_y— \qquad XI$$

e) der Reaktion der Amine der Formel IX, worin R_3 von H verschieden ist, mit den Ketonen der Formel $R_{12}CO(CH_2)_yR_4$ in Gegenwart von Ameisensäure, um die Verbindungen der Formel I zu erhalten, worin A eine Gruppe der Formel XI bedeutet;

f) durch Acylierung der Amine der Formel IX mit, z.B., substituierten Acylchloriden der Formel $R_{22}—COCl$, worin R_{22} eine Gruppe der Formel XII bedeutet

$$—(CH_2)_z—W—(CH_2)_y—E \qquad XII$$

worin E eine austauschbare Gruppe oder eine in eine austauschbare Gruppe überführbare Gruppe bedeutet und dann entweder (a) Reduzierung der so gebildeten Amide und anschließender Austausch der Gruppe E gegen die Gruppe R_4 oder (b) Austausch der Gruppe E gegen die Gruppe R_4 und Reduzierung der entstandenen Amide um die Verbindungen der Formel I zu erhalten, worin A eine Gruppe der Formel III ist, in der x z+1 ist.

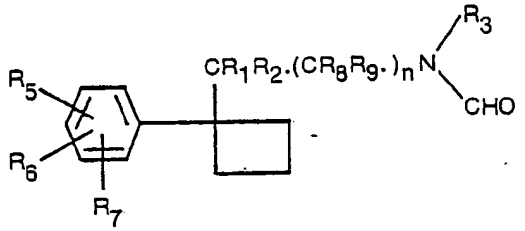
g) der Reaktion der Amine der Formel IX mit einer Verbindung der Formel XIII

$$H_2C=CH—G \qquad XIII$$

in der G die oben angegebene Bedeutung bezüglich R_4 oder bezüglich E aufweist und, wenn G die vorhin gegebene Bedeutung bezüglich E aufweist, Überführung der erhaltenen Verbindung in eine Verbindung der Formel I.

h) der Reaktion der Amine der Formel IX mit einer Verbindung der Formel XAR_4, in der X eine austretende Gruppe in Gegenwart einer Base bedeutet.

5. Verfahren zur Herstellung der Verbindungen der Formel I, in der R_3 H oder Methyl bedeutet, durch Reaktion der Formamide der Formel XIV

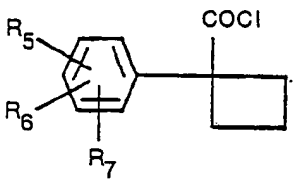


XIV

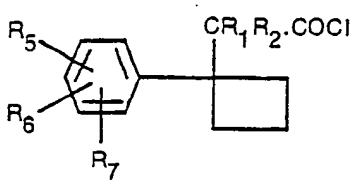
mit Aldehyden der Formel $R_{21}CHO$, worin R_{21} die vorhin gegebene Bedeutung aufweist, oder mit Ketonen der Formel $R_{12}CO(CH_2)_yR_4$ in Gegenwart von Ameisensäure, gefolgt von a) Hydrolyse der erhaltenen Formamide, um die Verbindungen der Formel I zu erhalten, worin R_3 H ist oder b) Reduzierung der erhaltenen Formamide, um die Verbindungen der Formel I zu erhalten, worin R_3 Methyl ist.

6. Verfahren zur Herstellung der Verbindungen der Formel I, bestehend aus der Reaktion der Amine der Formel VI mit Carbonsäureestern oder Säurechloriden, gefolgt von einer Reduzierung der entstandenen Amide.

7. Verfahren nach Anspruch 6, worin das Amin der Formel VI mit einem Säurechlorid der Formel XV oder XVI umgesetzt wird.



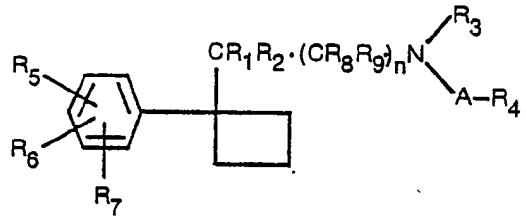
XV



XVI

Revendications pour les Etats contractants: BE CH DE FR IT LI LU NL SE

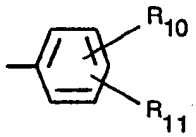
1. Composés de formule I



I

dans laquelle n = 0 ou 1;

dans laquelle lorsque n = 0, R_1 est H, un groupe alkyle à chaîne droite ou ramifiée contenant 1 à 6 atomes de carbone, un groupe cycloalkyle contenant 3 à 7 atomes de carbone, un groupe cycloalkylméthyle dans lequel le groupe cyclo alkyle contient 3 à 7 atomes de carbone, un groupe alcényle contenant 3 à 6 atomes de carbone, un groupe alcynyle contenant 3 à 6 atomes de carbone, un hétérocycle contenant un ou plusieurs hétéroatomes choisis parmi N, O et S, ou un groupe de formule II



II

dans laquelle, lorsque n = 1, R_1 est H ou un groupe alkyle contenant 1 à 3 atomes de carbone;

dans laquelle R_2 est H ou un groupe alkyle contenant 1 à 3 atomes de carbone;

dans laquelle R_3 est H ou un groupe alkyle à chaîne droite ou ramifiée;

dans laquelle A est un groupe de formule III

$$—(CH_2)_x—W—(CH_2)_y—$$ III

dans laquelle W est un atome d'oxygène ou un groupe de formule $—S(O)_m—$ dans laquelle m est 0, 1 ou 2, un groupe de formule $—CR_{12}R_{13}—$, un groupe cycloalkylidène contenant 3 à 6 atomes de carbone ou un groupe cycloalkylène contenant 3 à 6 atomes de carbone; x est 0 ou un entier de 1 à 5; y est 0 ou un entier de 1 à 5 (sous réserve que lorsque W est un atome d'oxygène ou un groupe de formule $—S(O)_m—$, x et y sont tous deux des entiers de 1 à 5); R_{12} et R_{13} qui sont semblables ou différents sont H, un groupe alkyle contenant 1 à 3 atomes de carbone, un hydroxy, un méthoxy ou un benzyle; dans laquelle R_4 est un cycle carbocyclique, un hétérocycle contenant un ou plusieurs hétéro-atomes choisis parmi N, O et S, un groupe cyano, un groupe carbamoyle de formukle $—CONR_{14}R_{15}$ dans laquelle R_{14} et R_{15} qui sont semblables ou différents sont H, un groupe alkyle contenant 1 à 3 atomes de carbone, ou R_{14} et R_{15} ensemble avec l'azote auquel ils sont fixés forment un hétérocycle, un groupe alcoxycarbonyle de formule $—COOR_{16}$ dans laquelle R_{16} est un groupe alkyle contenant 1 à 3 atomes de carbone, un groupe amido de formule $—N(R_{17})COR_{18}$ dans laquelle R_{17} et R_{18}, qui peuvent être semblables ou différents, sont des groupes alkyles contenant 1 à 4 atomes de carbone, ou R_{17} et R_{18} ensemble avec l'atome d'azote et le groupe carbonyle auxquels ils sont fixés forment un cycle, un groupe acyloxy de formule $—OCOR_{19}—$ dans laquelle R_{19} est un groupe alkyle contenant 1 à 3 atomes de carbone, un groupe hydroxy, un groupe thiol ou un groupe de formule $—OR_{20}$, $—SR_{20}$, $—SOR_{20}$ ou $—SO_2R_{20}$ dans laquelle R_{20} est un groupe alkyle à chaîne droite ou ramifiée contenant 1 à 4 atomes de carbone ou un groupe phényle éventuellement substitué;

dans laquelle R_5, R_6 et R_7 qui sont semblables ou différents sont H, un halogéno, un trifluorométhyle, un hydroxy, un groupe alkyle, un groupe alcoxy ou alkylthio, un phényle, ou R_5 et R_6 ensemble avec les atomes de carbone auxquels ils sont fixés, forment un second cycle benzène éventuellement substitué;

dans laquelle R_8 et R_9 qui sont semblables ou différents, sont H ou un groupe alkyle contenant 1 à 3 atomes de carbone;

dans laquelle R_{10} et R_{11} qui sont semblables ou différents, sont H, un halogéno, un groupe alkyle contenant 1 à 3 atomes de carbone ou un groupe alcoxy contenant 1 à 3 atomes de carbone;

et leurs sels pharmaceutiquement acceptables.

2. Composés de formule I comme revendiqué dans la revendication 1 dans laquelle R_1 est un groupe méthyle, éthyle, propyle, isopropyle, isobutyle, hexyle ramifié, cyclopropyle, cyclobutyle, cyclopentyle, cyclohexyle, cyclopropylméthyle, cyclobutylméthyle, cyclopentylméthyle, cyclohexylméthyle, allyl ou propynyle ou un hétérocycle choisi parmi un cycle furyle, thiényle, pyrrolyle, pyridyle, tétrahydrofuryle, tétrahydrothiényle, imidazolyle, pyrazolyle, pyrazinyle, pyrimidinyle, pyridazinyle, triazolyle, tétrazolyle, dithiannyle ou thiazolyle, ledit hétérocycle étant éventuellement substitué par un ou plusieurs groupes alkyles contenant 1 à 3 atomes de carbone, un ou plusieurs groupes halogéno, un ou plusieurs groupes alcoxy contenant 1 à 3 atomes de carbone ou un ou plusieurs groupes trifluorométhyle.

3. Composés de formule I dans laquelle W est un groupe de formule —$CR_{12}R_{13}$— et R_{12} est un groupe méthyle, éthyle ou propyle et R_{13} est H ou un groupe méthyle.

4. Composés de formule I comme revendiqué dans la revendication 1 dans laquelle R_4 est un groupe cyclohexyle, un groupe cycloheptényle ou un groupe phényle éventuellement substitué par un halogéno, un hydroxy, un alcoxy contenant 1 à 3 atomes de carbone ou un alkyle contenant 1 à 3 atomes de carbone.

5. Composés de formule I comme revendiqué dans la revendication 1 dans laquelle R_4 est un hétérocycle et est un furyle, thiényle, pyrrolyle, pyridyle, tétrahydrofuryle, tétrahydrothiényle, pyrrolinyle, pipéridyle, imidazolyle, pyrazolyle, pyrazinyle, pyrimidinyl, pyridazinyle, imidazolidinyle, imidazolinyle, pyrazolidinyle, pyrazolinyle, pipérazinyle, triazolyle, tétrazolyle, thiazolyle, isoxazolyle, morpholinyle, thiomorpholinyle ou les dérivés tétrahydro et dihydro de thiazolyle et d'isoxazolyle.

6. Composés de formule I comme revendiqué dans la revendication 1, dans laquelle R_4 est un groupe de formule —OR_{20} dans laquelle R_{20} est un groupe méthyle, éthyle, propyle, isopropyle, butyle ou isobutyle.

7. Composés de formule I comme revendiqué dans l'une quelconque des revendications précédentes dans laquelle R_5, R_6 et R_7 que peuvent être semblables ou différents sont choisis dans le groupe constitué par H et les groupes fluoro, chloro, bromo, iodo, méthyle, méthoxy et méthylthio ou R_5 et R_6 ensemble avec les atomes de carbone auxquels ils sont fixés forment un second cycle benzène éventuellement substitué par un ou plusieurs groupes halogéno, un ou plusieurs groupes alkyles contenant 1 à 3 atomes de carbone, un ou plusieurs groupes alcoxy contenant 1 à 3 atomes de carbone ou les substituants du second cycle benzène avec les atomes de carbone auxquels ils sont fixés forment encore un autre cycle benzène.

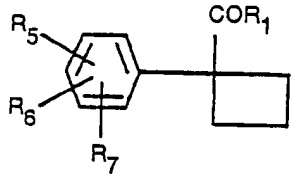
8. Composés de formule I comme revendiqué dans la revendication 7 dans laquelle les substituants sur le second cycle benzène sont des groupes fluoro, chloro, bromo, méthyle ou méthoxy.

9. Composés de formule I comme revendiqué dans la revendication 7 dans laquelle R_5 est un groupe halogéno, un groupe méthyle, un groupe méthylthio ou un groupe phényle et R_6 est H ou un groupe halogéno ou R_5 et R_6 ensemble avec les atomes de carbone auxquels ils sont fixés forment un second cycle benzène.

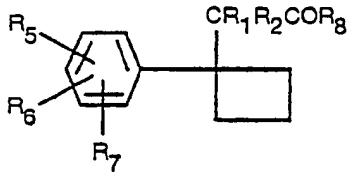
10. Compositions pharmaceutiques comprenant une quantité thérapeutique efficace d'un composé de formule I comme revendiqué dans l'une quelconque des revendications 1 à 9 avec un diluant ou support pharmaceutiquement acceptables.

11. Compositions pharmaceutiques comme revendiqué dans la revendication 10 sous forme d'une dose unitaire d'administration.

12. Procédé pour la préparation de composés de formule I comprenant l'amination par réduction d'une cétone ou d'un aldéhyde de formules IV ou V

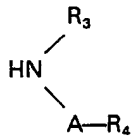


IV



V

par réaction de la cétone ou de l'aldéhyde avec une amine de formule VI



VI

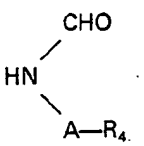
13. Un procédé comme revendiqué dans la revendication 12 dans lequel l'amination par réduction s'effectue:

a) par réaction de la cétone ou de l'aldéhyde avec l'amine de formule VI et réduction de l'imine ou de l'énamine obtenue par exemple avec du borohydrure de sodium ou du cyanoborohydrure de sodium,

b) par réaction de la cétone ou de l'aldéhyde avec l'amine de formule VI en présence d'un agent réducteur tel que le cyanoborohydrure de sodium ou, lorsque R_3 est autre que H, en présence d'acide formique,

c) lorsque R_1 et R_4 ne contiennent pas de double liaison réductible, par hydrogénation catalytique à température et à pression élevées, d'un mélange de la cétone ou de l'aldéhyde et de l'amine de formule VI.

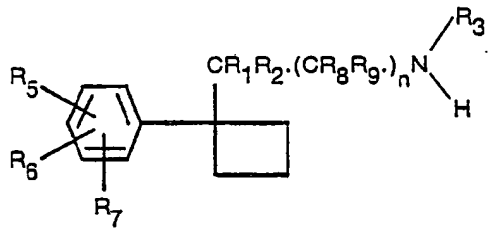
14. Procédé pour la préparation de composés de formule I dans laquelle R_3 est H ou un méthyle, comprenant l'amidation par réduction de cétones ou d'aldéhydes de formule IV ou V par réaction avec un formamide de formule VII



VII

en présence d'acide formique puis a) hydrolyse du formamide obtenu pour fournir les composés de formule I dans laquelle R_3 est H, ou b) réduction du formamide obtenu pour fournir les composés de formule I dans laquelle R_3 est un méthyle.

15. Procédé pour la préparation de composés de formule I à partir des composés de formule IX



IX

a) par acylation des amines de formule IX, par exemple par réaction avec un chlorure d'acyle de formule $R_{21}COCl$ ou un anhydride de formule $(R_{21}CO)_2O$ dans laquelle R_{21} est un groupe de formule X

$$—(CH_2)_z—W—(CH_2)_y—R_4 \qquad X$$

dans laquelle, lorsque W est un atome d'oxygène ou un groupe de formule $—S(O)_m—$, z est un entier de 1 à 4 et lorsque W est un groupe de formule $—CR_{12}R_{13}—$ ou un groupe cycloalkylène, z est 0 ou un entier de 1 à 4 et réduction des amides obtenus pour fournir les composé de formule I dans laquelle A est un groupe de formule III dans laquelle x est z+1,

b) par réaction des amines de formule IX avec les aldéhydes de formukle $R_{21}CHO$ et réduction des imines ou des énamines obtenues ou, lorsque R_1, R_2, R_4, R_{12} et R_{13} ne contiennent pas de double liaison réductible, par hydrogénation catalytique pour fournir les composés de formule I dans laquelle A est un groupe de formule III, dans laquelle x est z+1,

c) par réaction des amines de formule IX dans laquelle R_3 est autre que H avec les aldéhydes de formule $R_{21}CHO$ en présence d'acide formique pour fournir les composés de formule I dans laquelle A est un groupe de formule III, dans laquelle x est z+1,

d) par réaction des amines de formule IX avec les cétones de formule $R_{12}CO(CH_2)_yR_4$ et réduction des imines ou énamines obtenues ou, lorsque R_1, R_2, R_4 et R_{12} ne contiennent pas de double liaison réductible, par hydrogénation catalytique pour fournir les composés de formule I dans laquelle A est un groupe de formule XI

$$—CHR_{12}—(CH_2)_y— \qquad XI$$

e) par réaction des amines de formule IX dans laquelle R_3 est autre que H avec les cétones de formule $R_{12}CO(CH_2)_yR_4$ en présence d'acide formique pour fournir les composés de formule I dans laquelle A est un groupe de formule XI,

f) par acylation des amines de formule IX avec par exemple les chlorures d'acyle substitues de formule $R_{22}—COCl$ dans laquelle R_{22} est un groupe de formule XII

$$—(CH_2)_z—W—(CH_2)_y—E \qquad XII$$

dans laquelle E est un groupe remplaçable ou est transformable en un tel groupe, puis soit (a) réduction des amides ainsi formés puis remplacement du groupe E par le groupe R_4, soit (b) remplacement du groupe E par le groupe R_4 et réduction des amides obtenus pour fournir les composés de formule I dans laquelle A est un groupe de formule III dans laquelle x est z+1,

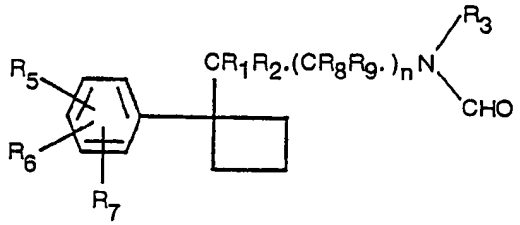
g) par réaction des amines de formule IX avec un composé de formule XIII

$$H_2C=CH—G \qquad XIII$$

dans laquelle G est comme défini ci-dessus relativement à R_4 ou relativement à E et, lorsque G a la signification définie ci-dessus relativement à E, conversion du composé obtenu en un composé de formule I,

h) par réaction des amines de formule IX avec un composé de formukle XAR_4 dans laquelle X est un groupe labile en présence d'une base.

16. Procédé pour la préparation des composés de formule I dans laquelle R_3 est H ou un méthyle, par réaction des formamides de formule XIV

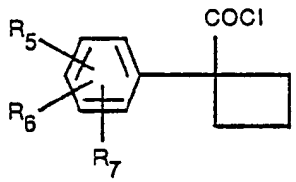


XIV

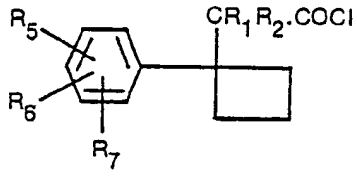
avec les aldéhydes de formule $R_{21}CHO$ dans laquelle R_{21} est comme défini ci-dessus ou avec les cétones de formule $R_{12}CO(CH_2)_yR_4$ en présence d'acide formique, puis a) hydrolyse du formamide obtenu pour fournir les composés de formule I dans laquelle R_3 est H ou, b) réduction du formamide obtenue pour fournir les composés de formule I dans laquelle R_3 est un méthyle.

17. Procédé pour la préparation des composé de formule I comprenant la réaction d'amines de formule VI avec des esters d-acide carboxylique ou des chlorures d'acide puis réduction de l'amide obtenu.

18. Procédé comme revendiqué dans la revendication 17 dans lequel on fait réagir l'amine de formule VI avec un chlorure d'acide de formule XV ou XVI



XV



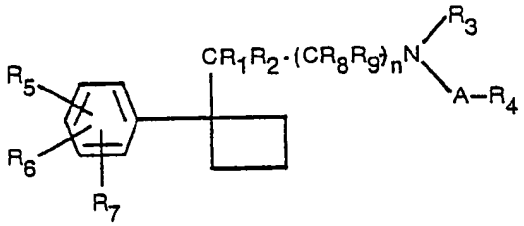
XVI

19. Composés de formule I comme revendiqué dans l'une quelconque des revendications 1 à 9 pour l'emploi dans le traitement de la dépression.

20. Compositions pharmaceutiques comme revendiqué dans la revendication 10 ou la revendication 11 pour l'emploi dans le traitement de la dépression.

Revendications pour l'Etat contractant: AT

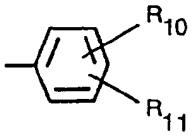
1. Procédé pour la préparation des composés de formule I



I

dans laquelle n = 0 ou 1;

dans laquelle lorsque n = 0, R_1 est H, un groupe alkyle à chaîne droite ou ramifiée contenant 1 à 6 atomes de carbone, un groupe cycloalkyle contenant 3 à 7 atomes de carbone, un groupe cycloalkylméthyle dans lequel le groupe cycloalkyle contient 3 à 7 atomes de carbone, un groupe alcényle contenant 3 à 7 atomes de carbone, un groupe alcényle contenant 3 à 6 atomes de carbone, un groupe alcynyle contenant 3 à 6 atomes de carbone, un hétérocycle contenant un ou plusieurs hétéroatomes choisis parmi N, O et S, ou un groupe de formule II



II

II

dans laquelle, lorsque n = 1, R_1 est H ou un groupe alkyle contenant 1 à 3 atomes de carbone;

dans laquelle R_2 est H ou un groupe alkyle contenant 1 à 3 atomes de carbone;

dans laquelle R_3 est H ou un groupe alkyle à chaîne droite ou ramifiée;

dans laquelle A est un groupe de formule III

$$—(CH_2)_x—W—(CH_2)_y—$$ III

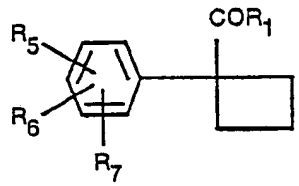
dans laquelle W est un atome d'oxygène ou un groupe de formule —$S(O)_m$— dans laquelle m est 0, 1 ou 2, un groupe de formule —$CR_{12}R_{13}$—, un groupe cycloalkylidène contenant 3 à 6 atomes de carbone ou un groupe cycloalkylène contenant 3 à 6 atomes de carbone; x est 0 ou un entier de 1 à 5; y est 0 ou un entier de 1 à 5 (sous réserve que lorsque W est un atome d'oxygène ou un groupe de formule —$S(O)_m$—, x et Y sont tous deux des entiers de 1 à 5); R_{12} et R_{13} qui sont semblables ou différents sont H, un groupe alkyle contenant 1 à 3 atomes de carbone, un hydroxy, un méthoxy ou un benzyle; dans laquelle R_4 est un cycle carbocyclique, un hétérocycle contenant un ou plusieurs hétéro-atomes choisis parmi N, O et S, un groupe cyano, un groupe carbamoyle de formule —$CONR_{14}R_{15}$ dans laquelle R_{14} et R_{15} qui sont semblables ou différents sont H, un groupe alkyle contenant 1 à 3 atomes de carbone, ou R_{14} et R_{15} ensemble avec l'azote auquel ils sont fixés forment un hétérocycle, un groupe alcoxycarbonyle de formule —$COOR_{16}$ dans laquelle R_{16} est un groupe alkyle contenant 1 à 3 atomes de carbone, un groupe amido de formule —$N(R_{17})COR_{18}$ dans laquelle R_{17} et R_{18}, qui peuvent être semblables ou différents, sont des groupes alkyles contenant 1 à 4 atomes de carbone ou R_{17} et R_{18} ensemble avec l'atome d'azote et le groupe carbonyle auxquels ils sont fixés forment un cycle, un groupe acyloxy de formule —$OCOR_{19}$— dans laquelle R_{19} est un groupe alkyle contenant 1 à 3 atomes de carbone, un groupe hydroxy, un groupe thiol ou un groupe de formule —OR_{20}, —SR_{20}, —SOR_{20} ou —SO_2R_{20} dans laquelle R_{20} est un groupe alkyle à chaîne droite ou ramifiée contenant 1 à 4 atomes de carbone ou un groupe phényle éventuellement substitué;

dans laquelle R_5, R_6 et R_7 qui sont semblables ou différents sont H, un halogéno, un trifluorométhyle, un hydroxy, un groupe alkyle, un groupe alcoxy ou alkylthio, un phényle ou R_5 et R_6 ensemble avec les atomes de carbone auxquels ils sont fixés, forment un second cycle benzène éventuellement substitué;

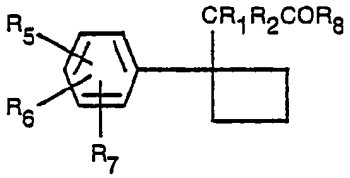
dans laquelle R_8 et R_9 qui sont semblables ou différents, sont H ou un groupe contenant 1 à 3 atomes de carbone;

dans laquelle R_{10} et R_{11} qui sont semblables ou différents, sont H, un halogéno, un groupe alkyle contenant 1 à 3 atomes de carbone ou un groupe alcoxy contenant 1 à 3 atomes de carbone;

comprenant l'amination par réduction d'une cétone ou d'un aldéhyde de formule IV ou V

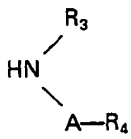


IV



V

par réaction de la cétone ou de l'aldéhyde avec une amine de formule VI



VI

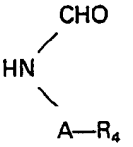
2. Procédé comme revendiqué dans la revendication 1, dans laquelle l'amination par réduction s'effectue:

a) par réaction de la cétone ou de l'aldéhyde avec l'amine de formuel VI et réduction de l'imine ou de l'énamine obtenue par exemple avec du borohydrure de sodium ou du cyanoborohydrure de sodium.

b) par réaction de la cétone ou de l'aldéhyde avec l'amine de formule VI en présence d'un agent réducteur tel que le cyanoborohydrure de sodium ou, lorsque R_3 est autre que H, en présence d'acide formique,

c) lorsque R_1 et R_4 ne contiennent pas de double liaison réductible, par hydrogénation catalytique à température et à pression élevées, d'un mélange de la cétone ou de l'aldéhyde et de l'amine de formule VI.

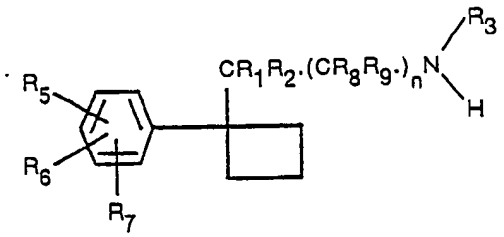
3. Procédé pour la préparation de composés de formule I dans laquelle R_3 est H ou un méthyle, comprenant l'amidaln méthyle, comprenant l'amidation par réduction de cétones ou d'aldéhydes de formule IV ou V par réaction avec un formamide de formule VII



VII

en présence d'acide formique puis a) hydrolyse du formamide obtenu pour fournir les composés de formule I dans laquelle R_3 est H, ou b) réduction du formamide obtenu pour fournir les composés de formule I dans laquelle R_3 est un méthyle.

4. Procédé pour la préparation de composés de formule I à partir des composés de formule IX



IX

a) par acylation des amines de formule IX, par exemple par réaction avec un chlorure d'acyle de formule $R_{21}COCl$ ou un anhydride de formule $(R_{21}CO)_2O$ dans laquelle R_{21} est un groupe de formule X

$$—(CH_2)_z—W—(CH_2)_y—R_4 \qquad X$$

dans laquelle, lorsque W est un atome d'oxygène ou un groupe de formule $—S(O)_m—$, z est un entier de 1 à 4 et lorsque W est un groupe de formule $—CR_{12}R_{13}—$ ou un groupe cycloalkylène, z est 0 ou un entier de 1 à 4 et réduction des amides obtenus pour fournir les composés de formule I dans laquelle A est un groupe de formule III dans laquelle x est z+1,

b) par réaction des amines de formule IX avec les aldéhydes de formule $R_{21}CHO$ et réduction des imines ou des énamines obtenues ou, lorsque R_1, R_2, R_4, R_{12} et R_{13} ne contiennent pas de double liaison réductible, par hydrogénation catalytique pour fournir les composés de formule I dans laquelle A est un groupe de formule III, dans laquelle x est z+1,

c) par réaction des amines de formule IX dans laquelle R_3 est autre que H avec les aldéhydes de formule $R_{21}CHO$ en présence d'acide formique pour fournir les composés de formule I dans laquelle A est un groupe de formule III, dans laquelle x est z+1,

d) par réaction des amines de formule IX avec les cétones de formule $R_{12}CO(CH_2)_yR_4$ et réduction des imines ou énamines obtenues ou, lorsque R_1, R_2, R_4 et R_{12} ne contiennent pas de double liaison réductible, par hydrogénation catalytique pour fournir les composés de formule I dans laquelle A est un groupe de formule XI

$$—CHR_{12}—(CH_2)_y— \qquad XI$$

e) par réaction des amines de formule IX dans laquelle R_3 est autre que H avec les cétones de formule $R_{12}CO(CH_2)_yR_4$ en présence d'acide formique pour fournir les composés deformule I dans laquelle A est un groupe de formule XI,

f) par acylation des amines de formule IX avec par exemple les chlorures d'acyles substitués de formule $R_{22}—COCl$ dans laquelle R_{22} est un groupe de formule XII

$$—(CH_2)_z—W—(CH_2)_y—E \qquad XII$$

dans laquelle E est un groupe replaçable ou est transformable en un tel groupe, puis soit (a) réduction des amides ainsi formés puis replacement du groupe E par le groupe R_4, soit (b) remplacement du groupe E par le groupe R_4 et réduction des amides obtenus pour fournir les composés de formule I dans laquelle A est un groupe de formule III dans laquelle x est z+1,

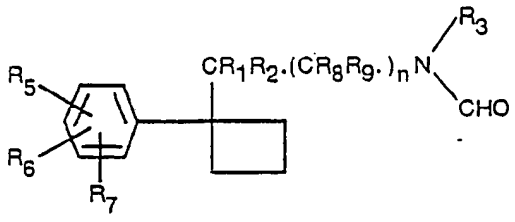
g) par réaction des amines de formule IX avec composé de formule XIII

$$H_2C=CH—G \qquad XIII$$

dans laquelle G est comme défini ci-dessus relativement à R_4 ou relativement à E et, lorsque G a la signification définie ci-dessus relativement à E, conversion du composé obtenu en un composé de formule I,

h) par réaction des amines de formule IX avec un composé de formule XAR_4 dans laquelle X est un groupe labile en présence d'une base.

5. Procédé pour la préparation des composés de formule I dans laquelle R_3 est H ou un méthyle, par réaction des formamides de formule XIV

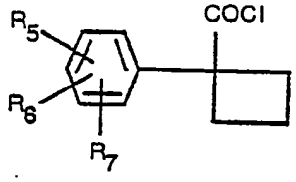


XIV

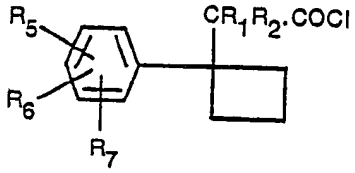
avec les aldéhydes de formule $R_{21}CHO$ dans laquelle R_{21} est comme défini ci-dessus ou avec les cétones de formule $R_{12}CO(CH_2)_yR_4$ en présence d'acide formique, puis a) hydrolyse du formamide obtenue pour fournir les composés de formule I dans laquelle R_3 est H ou b) réduction du formamide obtenu pour fournir les composés de formule I dans laquelle R_3 est un méthyle.

6. Procédé pour la préparation des composés de formule I comprenant la réaction d'amines de formule VI avec des esters d'acide carboxylique ou des chlorures d'acide puis réduction de l'amide obtenu.

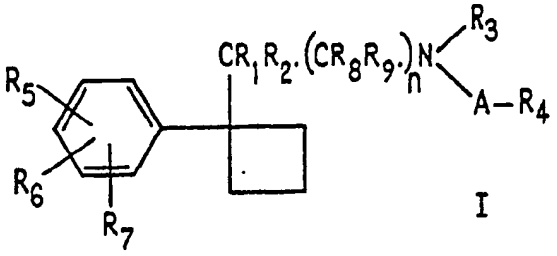
7. Procédé comme revendiqué dans la revendication 6 dans lequel on fait réagir l'amine de formule VI avec un chlorure d'acide de formule XV ou XVI



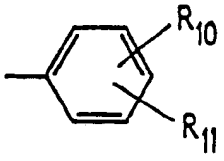
XV



XVI

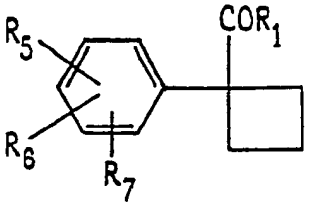


I

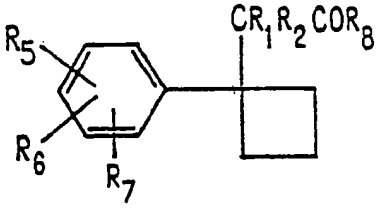


II

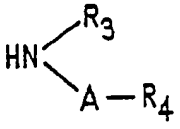
$-(CH_2)_x-W-(CH_2)_y-$ III



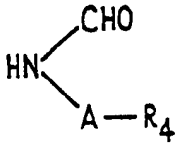
IV



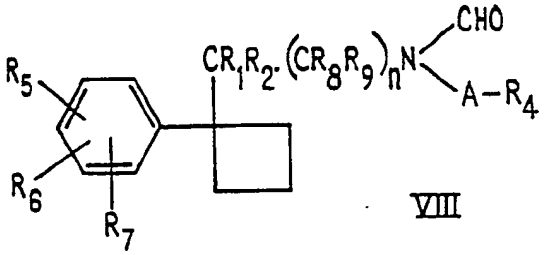
V



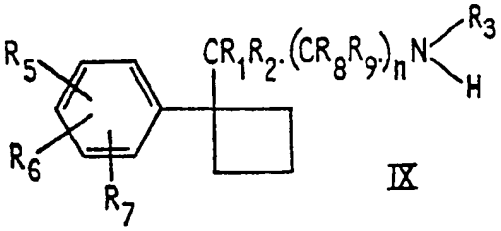
VI



VII



VIII



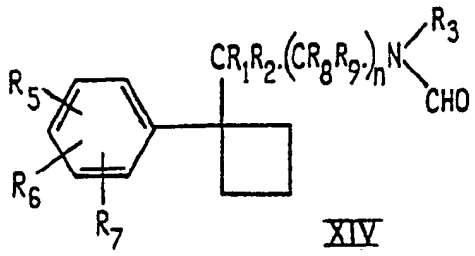
IX

$-(CH_2)_z-W-(CH_2)_y-R_4$ X

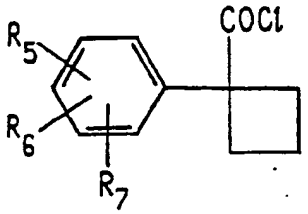
$-CHR_{12}-(CH_2)_y-$ XI

$-(CH_2)_z-W-(CH_2)_y-E$ XII

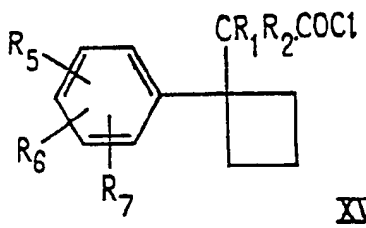
$H_2C=CH-G$ XIII



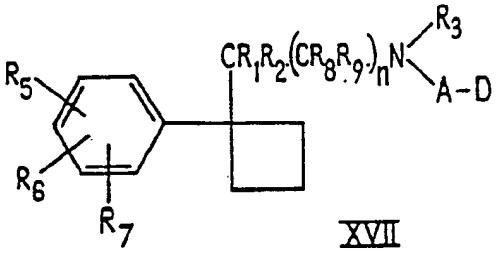
XIV



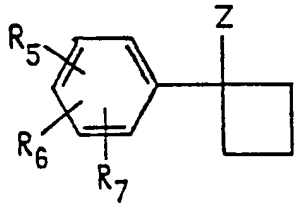
XV



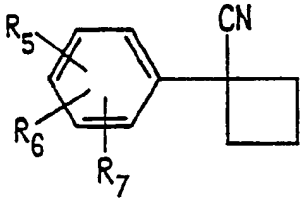
XVI



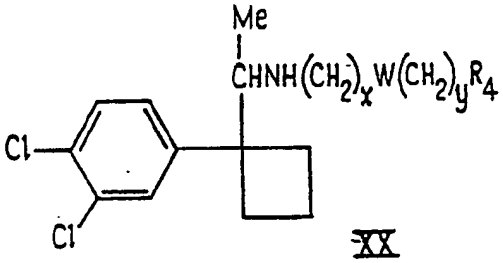
XVII



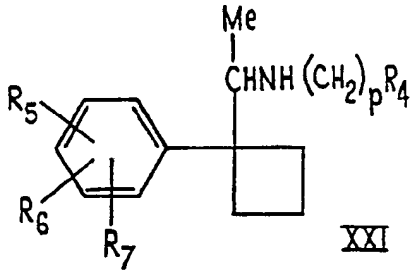
XVIII



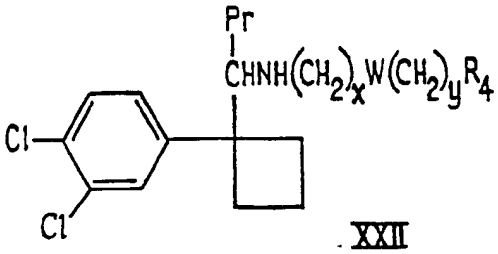
XIX



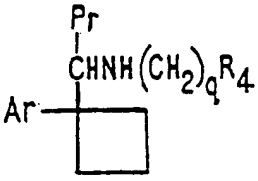
XX



XXI



XXII



XXIII